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ABSTRACT

This instructional module contains a description of the Human Genome Project (HGP). A discussion of issues in the philosophy of science and some of the ethical, legal, and social implications of research in genetics, and a survey of fundamental genetics concepts and of new, nontraditional concepts of inheritance are also included. Six instructional activities appropriate for high school and introductory college biology students, copy masters for the activities, and background information for students on each of the activities are provided. (DDR)

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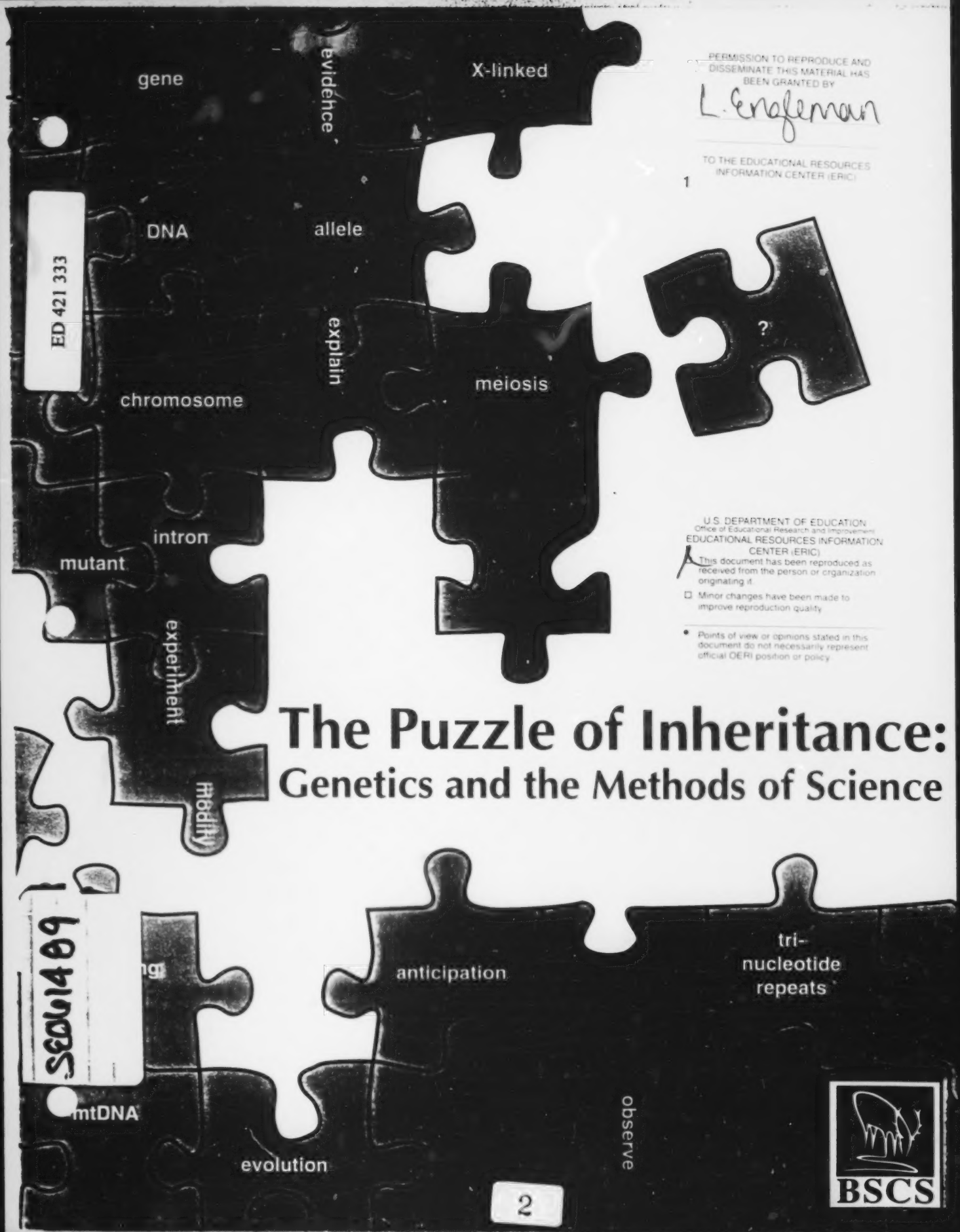

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The Puzzle of Inheritance:
Genetics and the Methods of Science

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THE PUZZLE OF INHERITANCE: GENETICS AND THE METHODS OF SCIENCE

Biological Sciences Curriculum Study (BSCS)
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Foreword

As biology teachers, you have two large tasks before you: to help your students gain a conceptual understanding of living systems, and to help your students understand the nature and methods of science. This second task, conveying to your students a fundamental grasp of the ways of science, is vitally important regardless of the future career choices your students will make. If they are to become informed citizens, able to appreciate and use the knowledge put before them, your students must understand the nature of scientific explanations and the power and rigor of the requirements of science.

Science assumes that the universe and the natural phenomena it encompasses are ordered and predictable. Scientific explanations reflect that assumption; they are driven by data that are collected carefully and analyzed rigorously. The data must be reliable; that is, the same data must result when other investigators repeat the original observations or experiments. Because science is a human endeavor, it is impossible (and perhaps not even wise) to eliminate all subjective judgments from the processes of science. The methods of science and scientific habits of mind, however, help to minimize the negative influence of subjectivity by holding all scientists and all scientific explanations to the same standards. If the corpus of scientific knowledge is to remain reliable, these standards must apply everywhere that science is done. From a school laboratory to the Pasteur Institute, from beginning students in North America to Nobel laureates from India, the requirements for valid scientific explanations do not change. In this sense, science may be as close as the world comes to a universal set of values.

We have designed this module to help convey some of these principles of science. We tested this module extensively and found it to be effective with high school and introductory college biology students. We hope you and your students find these materials interesting and helpful. We welcome your feedback and have provided a response form for that purpose. We look forward to hearing from you.

Joseph D. McInerney, Principal Investigator
B. Ellen Friedman, PhD, Project Director
Biological Sciences Curriculum Study (BSCS)

Summary of Contents

The module contains two major components. The first is the *Overview for Teachers*, which introduces the module, describes the Human Genome Project, and addresses issues in the philosophy of science and some of the ethical, legal, and social implications (ELSI) of research in genetics. This Overview also provides a survey of fundamental genetics concepts and of new, nontraditional concepts of inheritance. The second component, *Classroom Activities*, provides six instructional activities appropriate for high school or introductory college students. The first section of this component also is addressed to teachers; it contains specific suggestions for teaching each activity, including an annotated set of student materials. The other two sections of *Classroom Activities* are to be photocopied and distributed to students. *Use of instructional Activities 1-5 requires that students have completed a basic study of genetics such as is found in an introductory biology course.*

Evaluation Form for
The Puzzle of Inheritance: Genetics and the Methods of Science

Your feedback is important. *After you have used the module, please take a few minutes to complete and return this form to us.* (BSCS, Attn: HGN5, 5415 Mark Dabling Blvd., Colorado Springs, Colorado 80918-3842)

1. Please evaluate the *Overview for Teachers* by marking this form and providing written comments or suggestions on a separate sheet.

Sections used	not helpful				very helpful
I. Introduction	1	2	3	4	5
II. The Human Genome Project	1	2	3	4	5
III. The Methods of Science	1	2	3	4	5
IV. ELSI: Ethical, Legal, and Social Implications of Nontraditional Inheritance	1	2	3	4	5
V. Genetics: Basic Concepts and Nontraditional Inheritance	1	2	3	4	5
Glossary	1	2	3	4	5

2. Please evaluate the *Classroom Activities* by marking this form and providing written comments or suggestions on a separate sheet. Rate activities for their effectiveness at teaching NMS (nature and methods of science) concepts or genetics concepts.

Activities used	**NMS Concepts**					**Genetics Concepts**				
	not helpful				very helpful	not helpful				very helpful
Engage Activity	1	2	3	4	5	1	2	3	4	5
Activity 1	1	2	3	4	5	1	2	3	4	5
Activity 2	1	2	3	4	5	1	2	3	4	5
Activity 3	1	2	3	4	5	1	2	3	4	5
Activity 4	1	2	3	4	5	1	2	3	4	5
Activity 5	1	2	3	4	5	1	2	3	4	5

3. What are the major strengths of this module?

4. What are the major weaknesses of this module?

5. Please rate the overall effectiveness of this module: not effective very effective

1 2 3 4 5

6. Please provide a description of the classes in which you used this module: (circle response)

College: 2 year 4 year High school: grade 9 10 11 12

Freshman Sophomore Junior Senior Level of class: basic honors 2nd year

How many students used the module? _____ How many students per class? _____

Ethnicity: approximate % of minorities: _____

Description of school: _____

College: liberal arts science High school: urban suburban rural

7. Have you used BSCS materials before? ❒ yes ❒ no

Have you used the first BSCS genome module, *Mapping and Sequencing the Human Genome: Science, Ethics, and Public Policy*? ❒ yes ❒ no. If yes, please provide on a separate sheet feedback that you think will help us if we revise that module.

Have you used the second BSCS genome module, *The Human Genome Project: Biology, Computers, and Privacy*? ❒ yes ❒ no

8. Please provide your name and contact information below:

Name _____

School _____

Mailing address _____ ❒ home or ❒ work

_____

_____

Phone _____ ❒ home or ❒ work

FAX _____ ❒ home or ❒ work

E-mail address _____

Was the address on your mailing label for receipt of the module correct? ❒ yes ❒ no

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Overview for Teachers

This component introduces the module and provides a discussion of the Human Genome Project, the methods of science, and related ethical issues. It also reviews basic concepts in genetics, including some nontraditional explanations of inheritance.

Section I: Introduction

"Discovery is to see what everyone else has seen, but think what no one else has thought."

Albert Szent-Györgyi

Development of this curriculum project for high school and college biology classes grew out of the Human Genome Project (HGP), described in Section II of the *Overview for Teachers*. The HGP, a 15-year project, is an important step in our pursuit of knowledge about inheritance and about the role of genes in a variety of biological processes ranging from evolution to human health and diseases. Although the HGP is not conceptually novel, it provides a new level of understanding through its scope: a well-organized collection of genetic information now brings within reach many questions that previously were unaddressable. The motivation behind the HGP, then, is twofold. It is driven by the need for basic knowledge (a database containing maps and sequence data for entire genomes), and it is driven by applications of this knowledge, such as clinical studies. Not only does the HGP contribute to discoveries about genetics, it also is a significant landmark in the history of science. It involves a large-scale collaboration of many independent groups of scientists, and each group is interdisciplinary. Large scientific collaborations are not new—the physics installation near Geneva, Switzerland (CERN, the European Center for Nuclear Research) is one such example—but very large collaborations are unusual.

The primary job of HGP scientists is to locate and identify all the information stored in the human genetic material. (A photomicrograph of all 46 human chromosomes is presented in Figure 1.) In addition, the HGP will study the genomes of a variety of nonhuman organisms.

The HGP offers a fine opportunity to witness the dynamics of science. Those responsible for the structure of the HGP recognized that the impact of this large project will extend far beyond the genetics data alone, and they established the Ethical, Legal, and Social Implications (ELSI) component of the project to address these concerns. ELSI provides a mechanism to inform the public about the discoveries of the HGP and offers a way for the public to voice its interests and concerns about this work during the many years of the project. As part of the ELSI effort, the U.S. Department of Energy (DOE) has funded the development of this educational module, *The Puzzle of Inheritance: Genetics and the Methods of Science*, by the Biological Sciences Curriculum Study (BSCS).

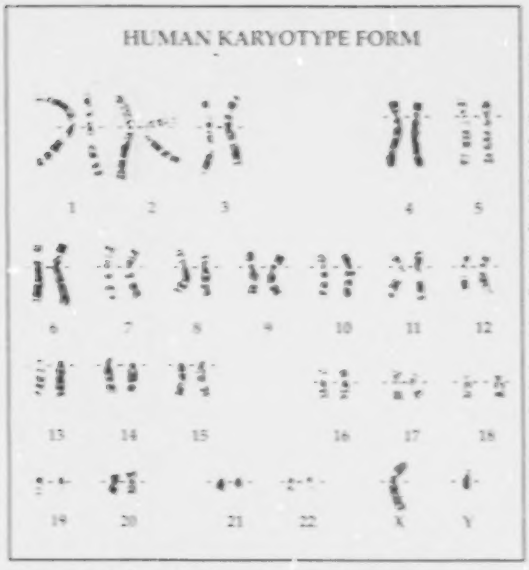
HUMAN KARYOTYPE FORM
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y
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Figure 1 A human karyotype: This photomicrograph shows the full complement of 46 human chromosomes arranged by size, banding pattern, and chromosome number. Notice that there are two copies of each of the 22 autosomes plus one copy of each type of sex chromosome (X and Y); this individual is a male.

Goals for the Module

This module is designed to meet the following goals:

- **The Nature and Methods of Science (NMS)** The first goal is to involve students in classroom activities that require explicit opportunities to apply scientific methods in a thought-provoking context, rather than as a cookbook-style list of steps. Students will glimpse the overarching nature of science in the process.
- **Concepts in Genetics** The second goal is to update the genetics curriculum to include some of the nontraditional concepts of inheritance that address processes not adequately explained by classical Mendelian genetics. It is, of course, our view of inheritance that is "nontraditional" rather than the genetic mechanisms themselves. Indeed, some nontraditional topics, such as mitochondrial inheritance and genomic imprinting, are widespread phenomena.
- **Professional Development** A third major goal is to provide an opportunity for professional development for teachers who want to expand their understanding of the methods of science, of ELSI topics and their application to the classroom, and of a variety of nontraditional explanations of inheritance. The *Overview for Teachers* provides a discussion of this information, and use of the *Classroom Activities* component of the module provides experience in communicating some of these topics. For some teachers, the activities-based approach to teaching also will be new.

Our rationale for these goals lies in the importance of a scientifically literate public and in the need for curriculum materials that support an inquiry-based approach to understanding the nature and methods of science. In addition, we recognize that although teachers have a perpetual need to keep abreast of new scientific knowledge, they have limited time to seek it out. We combined these goals because recent discoveries of nontraditional modes of inheritance exemplify the processes scientists use to test and expand scientific explanations. When coupled with selected episodes from the history of genetics, these newly discovered mechanisms of inheritance can provide compelling lessons in the nature of science.

> *"We can never require that science be productive; we can only require that it be sound."*
>
> J. Michael Bishop

Although this module touches on the history of genetics, particularly in Activities 1 and 3, we felt that we could not adequately present the history, the methods, and the overarching nature of science in one module. For this reason, we selected the methods of science as the main focus of our first goal, and we chose to present, to a lesser extent, the broader view of the nature of science as an endeavor with cultural ties. If you have time, we encourage you to extend your study of biology to include the history of genetics. If you choose to expand your treatment of the history and nature of genetics or other aspects of biology, you may find the publication titled *Teaching About the History and Nature*

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of Science and Technology (Social Science Education Consortium and BSCS, 1996[1]) useful to your plans. Students need to see that modern science is not "better than"—or indeed qualitatively different from—science of the previous several decades. Our limited presentation of some aspects of the history of genetics emphasizes that history extends beyond names and dates. Students can appreciate that current scientific knowledge is the product of an intellectual exploration, and one that continues to change. This module lets students see that scientific knowledge changes according to rigorous criteria, not by the whim of an influential individual or by popular consensus.

These materials were designed and written by curriculum developers at BSCS working with an external writing team and with the guidance of an advisory committee. In addition to external reviews by a group of specialists in teaching, bioethics, philosophy of science, and genetics, all materials in this module have undergone extensive, formal field testing to ensure their efficacy in the classroom (see Figure 2). The module was tested with more than 1,000 students at 14 high school and 2 college sites in the United States and Canada. Other high school and college teachers informally tested specific components of the module. We used the large body of evaluation data—combined with direct observations from site visits, external review data, and the recommendations of our advisory committee—to guide the revision (and in some cases rewriting) of the field-test materials in preparing this final version of the module. The module will be distributed free of charge to tens of thousands of high school and college biology teachers through the support of DOE.

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Figure 2 Field-test orientation: Teacher and writer John Zola conducts Activity 5 in an orientation session for field-test teachers at BSCS.

How to use the module

This module provides a detailed discussion for teachers (the *Overview for Teachers*) and six activities for students, complete with background material and suggestions for teaching (the *Classroom Activities*). The material contained in the *Overview for Teachers* is for your own use. It may extend your experience and thus be helpful for teaching the activities, but it is not essential to your use of the instructional activities. Figure 3 shows the layout of materials in these two components. Notice that within the *Classroom Activities* we provide these sections: the teacher pages (including annotated student material), special copymasters for each activity, and the regular student pages.

A summary of the six activities is provided in Figure 4. Notice that these include a brief activity to introduce the methods of science (Engage Activity) and five more classroom activities that combine experience with scientific methods and genetics topics. Time may not permit you to teach all six activities. We recommend that you introduce the module with the Engage Activity. You can use it early in the term, immediately prior to studying genetics, or immediately prior to

[1] Available from Social Science Education Consortium, Inc., P.O. Box 21270, Boulder Colorado 80308-4270; ISBN 0-89994-586-1.

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Overview for Teachers

I Introduction
II The Human Genome Project
III The Methods of Science
IV ELSI: Ethical, Legal, and Social Implications of Nontraditional Inheritance
V Genetics: Basic Concepts and Nontraditional Inheritance

Classroom Activities

I Teacher Pages
Engage, Activities 1-5

II Special Copymasters
Activities 1-4

III Student Pages
Engage, Activities 1-5

Figure 3 The module at a glance: The module consists of two large components, the *Overview for Teachers* and the *Classroom Activities*.

using the other activities in the module. For the major part of the module, choose any or all of Activities 1-5. We present them in the recommended sequence, but each activity is autonomous, and you can use the activities effectively in a different order. If you teach Activity 4 without Activity 3, you may need to augment information about trinucleotide repeats; if you teach both activities, keep them in sequence. The final activity, Activity 5, provides the best closure for the module and can serve as a performance assessment for evaluating student progress for the module as a whole. We recommend that you close with Activity 5 regardless of the other activities you have selected. The time required to teach all the activities is approximately 7 class periods of 50 minutes each. *Please note that Activities 1-5 require previous knowledge of fundamental principles of genetics.*

Along with each classroom activity, the module provides background material and annotations that offer strategies for the use of each activity. After you determine the activities you will use, you will need to copy the student pages, including worksheets and other supporting material provided as copymasters. Notice that the section for copymasters (hand-outs used at various points during an activity) is separated from the section for regular student pages (for which you will need one copy per student).

These materials take a constructivist approach to teaching. (For an introductory discussion of constructivism, see Trowbridge and Bybee, 1990.) This approach is based in part on forming a bridge from what students already know to what they will learn. The approach also helps students to be active partners in constructing their new knowledge rather than being told what they are to learn. The teacher *guides* students rather than simply *telling* them. The constructivist approach, which encourages inquiry, is apparent in this module in the way students are allowed to arrive at their conclusions in a step-wise fashion. For example, in Activity 2, the students use various data to build a concept of inheritance (mitochondrial inheritance) that is new to them. This approach to teaching takes more time than traditional lectures, but it generally leads to longer-lasting results. In addition, the active participation of students during the learning process increases the likelihood that students will apply what they learn to novel situations.

In addition to the *Classroom Activities*, the module provides a useful resource for teachers in the *Overview for Teachers*. You can use the *Overview for Teachers* as a stand-alone piece or as a supplement to the annotated activities to extend the background material provided for each activity. The Overview discusses some of the interests of philosophers of science and of bioethicists. The Overview also describes new discoveries in genetics that require nontraditional explanations of inheritance. The various sections of the *Overview for Teachers* go beyond the presentation of these topics in student pages. As the Human Genome Project and other areas of genetics progress, new information likely will emerge about the nontraditional examples of inheritance presented in this module, and, in time, these topics may become part of the standard biology curriculum. For now, these examples not only entice students (and teachers) with the prospect of new insights into genetics, they also demonstrate how science works.

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Figure 4 Summary of the activities

Engage Activity	Students are stimulated to think about the methods of science through a simple exercise of observation and measurement. This activity does not require knowledge of genetics.
Activity 1 **Standing on the Shoulders of Giants**	Students build a logical sequence of milestone explanations of inheritance based on conceptual connections rather than just chronology. Students also evaluate evidence for credibility and correlate evidence to milestone explanations. The activity provides a review of fundamental genetics concepts and stimulates discussion of the nature and methods of science.
Activity 2 **Puzzling Pedigrees**	Students study a collection of pedigrees to identify the inheritance pattern in each. Two pedigrees provide a special challenge: they show a pattern of inheritance that is not readily explained by traditional Mendelian concepts. Students formulate hypotheses and collect statistical data (coin flips) to test their hypotheses. They also read two brief articles that provide information about mitochondrial inheritance to help them build a new explanation. Finally, students record their ideas about the nature and methods of science.
Activity 3 **Clues and Discoveries in Science**	This activity is designed as a mystery. The task is to make discoveries about genetic anticipation. Students sort and analyze clues to build two pedigrees, one that shows a family history of Huntington disease and one for a family affected by myotonic dystrophy. Students look for patterns of disease onset and correlate those to molecular data related to trinucleotide repeats, thus building a nontraditional explanation of inheritance.
Activity 4 **Should Teenagers Be Tested for the Mutant HD Gene?**	The class reads a letter about the policy of withholding tests for Huntington disease from asymptomatic minors and conducts an ethical analysis in the form of a debate about the value of this policy.
Activity 5 **What Do We Know? How Do We Know It?**	The module concludes with a discussion of the differences between pseudoscience and science, using popular science and health claims. Students focus on observations about the methods of science made throughout the module. This activity provides a performance assessment for the entire module.

Section II: The Human Genome Project

"These are exciting and challenging times for biological researchers. The wealth of information and capabilities now being generated by the various genome projects and other biological endeavors will lead over the next two decades to more insights into living systems than have been amassed in the past two millennia. Biology is truly undergoing a revolution."

David A. Smith
(retiring director, Health Effects and Life Sciences Research Division, Office of Health and Environmental Research, DOE, 19 December 1996)

At the time this module was being developed, in the winter of 1996, the U.S. Department of Energy (DOE) held the fifth annual Contractor-Grantee Workshop. The workshop provided an opportunity for participants in the Human Genome Project (HGP) who are supported by DOE to report on and discuss their progress. Through a series of brief oral presentations and poster displays, participants built a picture of the current state of the project and discussed new collaborations that will further the effort. One of the most obvious characteristics of the event was the sense of cooperation among participants. The group was diverse, comprising geneticists and molecular biologists, biochemists and physical chemists, computer scientists, engineers, judges, lawyers, educators, and genetic counselors. The nature of the project requires the expertise of individuals from many disciplines, and the HGP has helped to spawn new areas of study, such as informatics, and new technologies, including capillary-based equipment for multiplex DNA sequencing. Here, we offer a brief overview of some key features of the work.[2]

What Is the Human Genome Project?

The Human Genome Project is a large, internationally coordinated effort in biological research directed at creating a series of maps of the DNA of humans and several other species, with each map providing greater detail (resolution). Figure 5 shows the rate of progress

[2] A more detailed description of the fundamental techniques and background for the HGP is available in the first two genome curriculum modules that BSCS developed through DOE funding. The first module is a print curriculum titled *Mapping and Sequencing The Human Genome: Science, Ethics, and Public Policy*. The second module, *The Human Genome Project: Biology, Computers, and Privacy*, combines print and software.

of the different aspects of the work on the human genome. The project is large in scope, time line, and funding. The U.S. Department of Energy and the National Institutes of Health (NIH) have jointly defined the project as a 15-year effort that began in 1990, with funding estimated at $3 billion. The ultimate goal is to map and sequence all of the estimated 80,000 human genes. The genetic map will be at a resolution of 2Mb, and the physical map will be at a resolution of 0.1Mb (Mb is a megabase, or 1 million nucleotides). Additional goals are to collect the human genome as clones of approximately 5kb in length and ultimately to resolve a base-by-base sequence (kb is kilobase, or 1,000 nucleotides). Additional material is presented in the *Primer on Molecular Genetics*, which focuses on techniques. This publication was produced by DOE as a part of the HGP. For information about the primer, contact the Human Genome Management Information System, Oak Ridge National Laboratory, P.O. Box 2008, Oak Ridge, TN 37831-6050, phone (615) 574-7582, Internet: yustin@ornl.gov.

Detailed maps of the genomes of several other well-studied organisms also are being made. These organisms include several bacterial species (such as *Mycoplasma genitalium*, *Haemophilus influenzae*, *Methanobacterium thermoautotrophicum*, *Bacillus subtilis*, *Pyrobaculum aerophilum*, *Methanococcus jannaschii*, and *Escherichia coli*), yeast (*Saccharomyces cerevisiae*), nematode (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), mouse (*Mus musculus*), and a flowering plant (*Arabidopsis thaliana*). By including organisms other than humans, the HGP provides a wealth of data for evolutionary research in addition to the valuable foundation of genetics information for each species studied.

Who Is Doing the Human Genome Project?

The HGP includes a wide variety of professionals in science, education, ethics, medicine, law, engineering, computing, and mathematics. Hundreds of research laboratories contribute, and some large

Figure 5 Progress on the HGP: The rate of each level of inquiry is depicted.

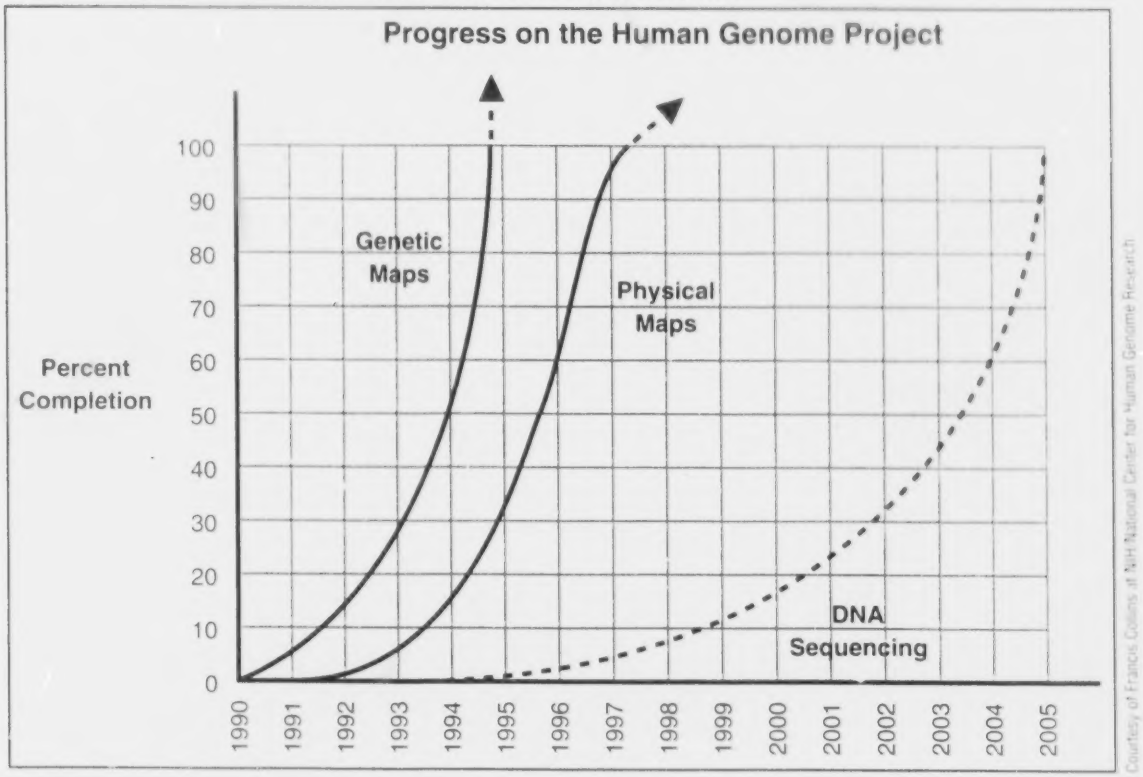

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Figure 6 Human Genome Program Centers (as of June 1996)

Center	Research Focus
Baylor College of Medicine	Physical mapping; emphasis on chromosomes 6, 15, 17, X
Children's Hospital of Philadelphia	Genetic and physical maps of chromosome 22
Lawrence Berkeley Laboratory	Physical map of chromosome 21; improvements in sequencing automation and informatics
Lawrence Livermore National Laboratory	Genetic and physical maps of chromosome 19 (completed)
Los Alamos National Laboratory	Maps of chromosome 16; techniques for high-speed mapping and sequencing (completed)
Stanford University	Maps of chromosome 4
University of California, Berkeley, Drosophila Genome Center	Physical map of the Drosophila genome
University of Iowa Cooperative Human Linkage Center	Expansion of the genetic linkage map for the entire human genome
University of Texas Health Science Center at San Antonio	Maps of chromosome 3
University of Utah	Development of genomic technologies
Washington University School of Medicine	Maps of chromosomes 7 and X; sequencing of C. elegans genome
Whitehead Institute for Biomedical Research and Massachusetts Institute of Technology	Maps of the mouse genome; STS map of the entire human genome
E. coli Genome Project, University of Wisconsin	Sequencing the chromosome of Escherichia coli

Human Genome Program Centers help focus and coordinate the work. Involvement of different centers changes as the project proceeds. Figure 6 lists some of the genome centers and the focus of their work. For an update, consult the DOE web site at http://www.ornl.gov/hgmis or the NIH web site at http://www.nchgr.nih.gov.

In addition to direct efforts to map and sequence particular human chromosomes or those of model organisms, these centers improve existing technologies and develop new technologies to increase the speed, accuracy, and cost-effectiveness of the HGP. These centers also act to stimulate and coordinate collaboration among investigators not formally associated with the HGP. The work is not limited to the United States. The Human Genome Organization (HUGO), formed in 1988, coordinates international scientific collaboration between Canada, the United States, Italy, the United Kingdom, France, the Commonwealth of Independent States, the European Community, and Japan. The United Nations Educational, Scientific, and Cultural Organization

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(UNESCO) promotes the continued involvement of developing nations in genome activities and also supports international conferences and exchanges.

How is the Human Genome Project Related to the Nature of Science?

As David Smith's quote (p. 9) indicates, the Human Genome Project is expanding our collection of genetic data enormously. Simply mapping and sequencing the entire human genome will not, however, provide us with answers to all of our questions about genetics. Knowing the sequence of a stretch of DNA or its location on a given chromosome does *not* reveal the significance of the region. If the region encodes protein, the DNA sequence will predict accurately the corresponding amino acid sequence of the protein, but neither sequence will tell us the *biological function* of the protein in the absence of additional data. Fortunately, much is known about the biological function of various proteins, and data are accumulating rapidly. With the foundation of a detailed and organized bank of genome data, biologists can construct a more complete picture of living systems.

Although the HGP will not answer all questions about genetics, it will provide an invaluable databank. In addition, as they collect data, researchers have made and will continue to make discoveries about specific genes, the organization of genetic information, evolutionary relationships at the molecular level, and new technologies in laboratory and computer applications. The genome map and sequence data will serve as powerful tools for future research in genetics, evolution, and medicine, in this way fueling the work of scientists in years to come.

The HGP also provides a classic demonstration of the nature and methods of science. For example, the HGP shows one aspect of the nature of science—intermarriage of technology and science—in several ways. The decision to begin the HGP was based in part on the availability of new technologies for cloning and sequencing DNA and for storing and analyzing huge amounts of map and sequence data. The HGP continues to pursue and produce impressive new technologies for these purposes.

The HGP illustrates the power of cooperation among groups of researchers and among professionals who have different types of expertise. This large project shows the way in which new work is built on old work. The vast pre-existing body of knowledge about the behavior and location of many genes in the organisms being studied is a critical resource for the mapping and sequencing of the genome of each of these species.

The existence of the ELSI program is testimony to the social context of scientific research. Society's concerns about genetic disorders such as cystic fibrosis and Huntington disease help to guide decisions about those areas of research that the HGP will support and pursue. In addition, the ELSI component of the HGP shows the concern of the project's directors and participants to acknowledge and explore the impact of this work on society.

(Reports on progress in specific scientific and ELSI areas of the HGP show the rapid change in knowledge as a result of this work. A special Genome Issue of the publication *Science* [Vol. 274, 25 October 1996] provides the latest available update as this module goes to press.)

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Section III: The Methods of Science

"The power of accurate observation is often called cynicism, by those who do not possess it."

George Bernard Shaw

"The goal of science is not to open the door to everlasting wisdom, but to set a limit on everlasting error."

Galileo,
in the Bertolt Brecht play, *Galileo*

As thinking organisms, humans constantly observe and consciously interpret the world around them. Science offers a rigorous method of investigating the natural world, a method that is based on careful observation and well-reasoned argument that includes the formation and testing of hypotheses. Science has demonstrated remarkable power to describe the natural world accurately and to identify the underlying causes of natural phenomena.

Treatment of the Methods of Science in this Module

Scientific knowledge endures because of the strength of the methods used to obtain it. The instructional activities provided by this module demonstrate the durability of scientific concepts and scientific methods. Some activities deal with genetics concepts never mentioned or observed by Gregor Mendel in his nineteenth-century work, yet these new discoveries also involve the fundamental principles of genetics that he did report. New discoveries sometimes refute pre-existing scientific explanations of natural processes, but much more often they refine or expand prior knowledge. New work generally builds on old work rather than razing the site.

Too often the methods of science are presented as a set of steps to be memorized. Students recite them by rote, with little understanding and less application. This module takes a very different approach, providing activities that help students *experience* the methods of science and *connect* these methods with events in their own lives. Presentation of the methods of science is interwoven into the learning experience that reveals new concepts in genetics. Activity 5 is designed specifically to help students connect their science process skills with familiar events outside the classroom.

The Goals of Science and Methods Used to Meet Them

In this section of the module we present a discussion of the goals of science in order to provide a context for the discussion of scientific methods. In addition,

we discuss the rationale for, and benefit of, the rigorously disciplined methods of science. The initial discussion of the nature and methods of science (NMS) is framed around six questions, summarized in Figure 7. These questions reappear in various ways throughout the student activities and are used for student assessment in Activity 5.

This discussion of the methods of science is not exhaustive; rather, it builds a view of science in the language of questions and concerns that arise in the laboratory and in the classroom. Please keep in mind that this view of science is not new; early geneticists used these methods, for example. The fact that Mendel used rigorous scientific methods and criteria to guide his work is the reason that Mendelian genetics continues to provide reliable explanations for many of the fundamental processes of inheritance. These same methods that have recently brought to light some intriguing "nontraditional" explanations of genetic mechanisms will guide future scientists to new discoveries that will continue to change our understanding of inheritance.

Figure 7 A snapshot of the goals and methods of science

1. What does science try to do?
- Science tries to provide causal explanations for natural phenomena.

2. How do we know that causal explanations are on the right track?

Causal explanations are on the right track when
- they demonstrate predictive power;
- other observations (evidence) rule out competing causal explanations.

3. What counts as evidence in science?

Evidence in science includes
- empirical data;
- existing explanations about related phenomena that are supported by independent data.

4. What makes science objective?
- Science is conducted by a rigorous set of methods.
- Authority and fame by themselves are not sufficient to establish the scientific validity of an explanation.

5. How and why does scientific knowledge change?
- Scientific explanations always are open to change.
- New evidence may show that an existing explanation is inadequate and that it needs to change.

6. What is the difference between pseudoscience and science?
- Pseudoscience fails to meet the intellectually rigorous requirements of science.
- Internal consistency sets scientific knowledge apart from pseudoscience.

1. What does science try to do?
- Science tries to provide causal explanations for natural phenomena.

Science is an organized pursuit of knowledge pertaining to natural processes. Often, science seeks to provide causal explanations of those processes. (Another term for a scientific explanation is "hypothesis." A hypothesis is a scientific explanation that is based on evidence, that is intended to account for some aspect of a natural process, *and that can be tested*.) A causal explanation proposes an account of the processes and mechanisms that produce a given biological phenomenon. One must establish a logical or meaningful connection between a phenomenon and the event purported as its cause, and this connection is made through observation, through testing (which often includes experimentation), and, often, through statistical analysis. These rigorous steps are necessary to distinguish the actual causes from randomly or coincidentally associated events.

It is not easy to establish causality. People who do not employ scientific reasoning, however, sometimes mistakenly assume that one event is the cause of a second event solely because it precedes the second event. Science requires a much stronger association to establish a causal process. A classic example from folklore states that eating strawberries while pregnant can cause birthmarks on one's newborn child. The timing of the putative cause (eating strawberries) precedes the observed result (birthmark), but there is no credible and relevant evidence to support the first event as a *cause* of the second one.

Constant and regular temporal association of events supports the proposal of a causal relationship, but science requires further analysis. Geneticists use statistical methods to test large sets of evidence to determine whether their regular and constant association occurs more frequently than chance would predict. Scientists also look for a step-wise biological process

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that starts with the cause and ends with the observed effect. An example is a mutation in the gene phenylalanine hydroxylase. If an individual is homozygous for this mutation, the enzyme will be deficient, blocking the metabolism of phenylalanine to tyrosine. Phenylalanine is converted through an alternate pathway to phenylpyruvic acid and other metabolites that can cause mental retardation, one symptom of the disorder phenylketonuria (PKU). The associations between these steps are well established; they constitute valid evidence for the genetic causation of PKU. Evidence for a causal relationship also is strengthened when it is observed by more than one person and when other lines of evidence point to the same conclusions. A good explanation of causation also displays the power to predict the outcome of related events accurately.

The causes of biological phenomena are complex and diverse, and we build our understanding of them in stages. Explanations often begin with simple, accurate observations that do not immediately attempt to address causation. This point is brought out for students in the Engage Activity of this module. Generally, however, scientists are looking for clues to the mechanisms that underlie specific biological processes, and they begin to build an understanding of these processes by explaining whatever mechanisms are accessible to their observation at a given time. This approach is analogous to teasing out the threads in a knot; it is easier and more efficient to attack the knot bit by bit rather than trying to untie it all in one motion.

The more fully we identify various aspects of the causes of a given phenomenon, the more we reinforce the validity of our explanation. As we unravel new layers in a scientific puzzle, through new observations or new reasoning, we test new explanations against existing knowledge. If a new explanation *is consistent* with previous knowledge, then the new work reinforces the validity of the earlier work. If, however, the new explanation is *not consistent* with extant knowledge, we must either discard the new explanation, or revise the prior knowledge.

One key point to consider for students is their perception of the word "theory." Students often mistakenly think that this word means about the same as an ephemeral guess or a hunch; they see a theory as an unsubstantiated idea. A reference called *Usage and Abusage, A Guide to Good English* (Partridge, 1994) states that "theory is occasionally used loosely... where ***expectation*** or ***opinion*** would be preferable." For instance, a student might say, "In theory, I should do well on tomorrow's test." The actual meaning of a theory ***in a scientific context*** is very different, and you need to emphasize this point explicitly for students. A theory, as scientists use the term, refers to a large-scale explanation, or series of explanations, that describes the causes of many natural processes (Rosenberg, 1985). An accepted scientific theory is very well substantiated by evidence, it has been built logically upon valid assumptions, and it has been extensively tested. If a theory were not substantiated, it would not be taken seriously by the scientific community, no matter who proposed it. A scientific theory is not established nor refuted on the basis of personal opinion that fails to follow the discipline of scientific methods; rather, a theory is an explanation of far-reaching significance so well tested and supported by such an abundance of credible evidence that it becomes a broadly accepted and fundamental scientific concept. There are a number of powerful theories in biology: for example, cell theory, chromosome theory, germ theory, and the theory of evolution. Each is supported by overwhelming amounts of evidence. The following discussion describes the role of evidence and testing in the process of building scientific explanations.

2. How do we know that causal explanations are on the right track?

Causal explanations are on the right track when

- they demonstrate predictive power,
- other observations (evidence) rule out competing causal explanations.

The short answer is that explanations are on the right track when they enable us to predict what we can later observe. This simple statement describes a powerful property of scientific explanation. By "predict," scientists mean something very specific: the ability to describe accurately and in precise detail an outcome of a particular natural event based on the explanation of the cause or causes of that event. Observation confirms the accuracy of the prediction.

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For example, if we hypothesize that a particular DNA sequence functions as an enhancer of transcription, we might predict that inserting that sequence next to a gene will increase the amount of messenger RNA produced from that gene. This outcome is testable, observable, and, indeed, quantifiable. If the amount of RNA does increase, this observation reinforces the hypothesized causal role of the enhancer sequence.

Prediction in the scientific sense need not be solely about future events. Instead, we can ask whether a proposed causal explanation would have predicted phenomena that have already happened and can be observed. By "predict" we mean that the explanation is consistent with the observed outcome. For example, the explanation of genetic code lets a scientist predict how a particular point-mutation in a DNA sequence will have altered the amino acid order in the encoded protein. By checking the actual amino acid sequence of the mutant gene product, the results can confirm or refute the predictive power of the explanation.

Although accurate prediction helps to validate that an explanation is on the right track, an accurate prediction is not by itself sufficient for this purpose. Two other criteria are important: a) we must rule out competing explanations of what we observe before we can be confident that we have the correct cause, and b) we must ensure that the proposed causal explanations are consistent with what we know about related biological processes or other areas of knowledge, such as chemistry or physics. In some cases, only a partial answer is possible because the available data provide insight into a limited number of possible explanations. Perhaps the investigator can eliminate all but two or three explanations. Such scientific work has considerable value in that it simplifies the questions to be addressed in future work and allows scientists to focus their energies and resources on the most promising lines of inquiry.

Ideally, competing explanations will be inconsistent with the observed data, but still other criteria must be met before we can accept an explanation as valid. A proposed causal hypothesis that predicts the data but that is highly implausible on other grounds is not well confirmed. In other words, a valid explanation must be based on the combination of credible evidence that is relevant to the hypothesis in question, on sound reasoning, and on reliable assumptions. Here, "relevant" means that the evidence has a rigorous connection with the idea being tested, either to support or refute it. A conclusion or inference that does not follow from the premise is a *non sequitur*, and it is not relevant evidence. An example of correct but irrelevant evidence is found in Activity 1 with regard to sex determination; the observation that human females produce fewer gametes than do human males is correct, but it does not address the issue at hand.

In summary, we know a scientific explanation is on the right track when we can answer "yes" to the following questions:

- Does the proposed causal mechanism predict what we observe?
- Does no other causal mechanism predict or fit with that data?
- Is our hypothesis reasonable given scientifically reliable knowledge about other related areas of biology (or any other science)?

> *"The great tragedy of science: a beautiful hypothesis destroyed by an ugly fact."*
>
> T.H. Huxley

One of the strengths of a scientific explanation is that it is testable. Indeed, explanations that cannot be tested do not count as scientifically valid. The ideas discussed in the preceding paragraphs explain why controlled experiments are important, particularly to establish a causal relationship. If we propose that A causes B, in the ideal case we would like to hold everything fixed or unchanged except A. Then we can change or manipulate A and observe the consequences. If B changes only when A does, we have good evidence that A causes B.

Controlled experiments in the laboratory attempt to get as close to the above ideal as possible, although no laboratory experiment literally controls or holds fixed every possible confounding factor. For example, if you were studying the effects of light on plant growth, you might design an experiment in which you keep water and temperature constant and vary

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light intensity. You have not, of course, controlled potential fluctuations in seismic activity, air pollution, or solar flare activity. Only the major and obvious factors are addressed. Moreover, laboratory experiments are not the only way to answer scientific questions. Observation of naturally occurring events, without manipulation by the investigator, can help determine the extent to which an explanation is on the right track. In short, nature provides us with "natural experiments." These kinds of tests are widespread in science—cosmology and astronomy rely on them heavily, as does, of course, biology. Often, students think of evidence as being exclusively the property of manipulated experiments. It is important to help students appreciate the power of careful observation of natural events. Much of the initial work of mapping and sequencing in the Human Genome Project is essentially observational.

3. What counts as evidence in science?
Evidence in science includes

- empirical data, and
- existing explanations about related phenomena that are supported by independent data.

Evidence in science is based on rigorous observations that must meet the criterion of being publicly observable. The fact that others can confirm or refute what you claim to observe provides a crucial test of the scientific validity of your explanation. Rumor, speculation, mystical experiences, and other unsubstantiated information are not accepted as credible scientific data. Students usually can recite that scientific experiments must be "repeatable," but it is important to challenge students to describe what that statement actually means. Experimental results that are observable by other investigators have the highest scientific merit. If an experiment or observation is repeated by the same or another person, and if the resultant data are the same, the credibility of that evidence improves.

Evidence is more compelling in its ability to support an explanation when the following are true:

a. *An explanation is strengthened when we have multiple lines of evidence—that is, when we have evidence from different sources.* Different lines of evidence for the same hypothesis reduce the likelihood that we ignored confounding factors or that we spuriously concluded that our hypothesis predicts the observable data.

b. *The more precise our data are and the more precisely our causal hypotheses predict what we observe, the stronger is our evidence.* To meet these conditions, a hypothesis must be stated carefully, particularly avoiding a focus that is too broad. If the scope of a hypothesis is excessive, too many factors come into play, and it is difficult to design meaningful tests that rule out confounding causes. That is why one of the most important skills in science is the ability to ask a *good* question, that is, a question that is precise and that one can investigate by focusing on one or a few variables. For example, although biologists investigate the nature of life, they do not conduct experiments that ask the broad question, "What is life?" They ask, rather, more concise questions that address components of the larger question. For example, these questions are more addressable:
   - What are the major macromolecules found in living systems?
   - What happens to a cell if we remove its genetic material?
   - What genes must be present for a cell to function properly?

Students often have trouble delineating their questions for term papers or science fairs. You should help them understand that good science begins with a good question.

In addition, if our data are imprecise, then we should have less confidence in our conclusions. An imprecise observation, such as "The bacterial population increased quickly," is much less useful than is a quantitative observation, such as "The population size doubled in 33 minutes." A hypothesis may fail to predict the observed data because those data are inaccurate. If a hypothesis fits with data we know to be inaccurate, we must lose confidence in the validity of the hypothesis in question.

c. *Evidence also comes from the application of knowledge gained through previous work.* Hypotheses that already have been tested successfully can and should be used as background knowledge for testing the validity of new causal explanations. A successful test provides reinforcement of

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previous conclusions at the same time that it helps to establish the new idea. A test that fails should lead us to re-examine the old, as well as the new, idea. This situation should cause us to consider modifying existing concepts if sufficient data warrant the change. Scientific hypotheses usually make reference to other scientific explanations, and consistency between explanations is required. Indeed, internal consistency of scientific explanations is an important criterion for validity.

4. What makes science objective?

- Science is conducted by a rigorous set of methods.
- Authority and fame by themselves are not sufficient to establish the scientific validity of an explanation.

The world exists, regardless of our knowledge of it; science strives to achieve a description of the natural world that accurately reflects reality. A scientist may want to believe that his or her preferred hypothesis is correct, but nature does not have to cooperate. Scientific methods are designed to make the correlation between reality and our descriptions of reality as close as is possible, considering that the descriptions are built by humans with limited senses and within the limited time available to explore the universe. Scientific understanding of a natural process usually is built in stages. For example, investigators recognized the existence of blood as a liquid and the presence of cells floating in that liquid before they identified hemoglobin as the molecular carrier of oxygen in red blood cells. Each stage of investigation narrowed the gap between the reality of how oxygen was being transported and our knowledge of that process. The earliest views were incomplete, but the fact that they were derived using rigorous scientific criteria resulted in their durability: liquid blood in our vessels does, indeed, carry oxygen throughout the body, and continued research has revealed many details of the process.

Even when scientists attempt to be completely objective, they may find it difficult to do so. Our senses are limited, although technologies greatly expand what we can detect. We also are influenced by our emotions, by societal views, by economics, and by job pressures.

Scientific theories are built according to a rigorous, disciplined process, but theories may not be perfect reflections of nature. The possibility for this discrepancy underlines the need for rigorous criteria in construction of scientific explanations. The methods of science include the requirement for publicly observable and repeatable evidence, the testing of an explanation by prediction and observation, the connection between existing and new explanations, and the requirement to rule out competing explanations. These methods provide a standard that helps prevent individual scientists from finding only what they *want* to see, whether consciously through ambition and pride, or subconsciously. The system is not perfect. The particular path that discovery takes is influenced by human values, particularly because cultural views often determine to which arenas of work research funds will be directed. The methods of science, however, are powerful—though not foolproof—safeguards that help to limit the impact of bias and subjectivity in the acquisition and application of scientific knowledge. A system planted on a firm foundation of valid premise, sound reasoning, and credible evidence has the ability to endure.

The collective nature of science also encourages objectivity in the field. The results of individual scientists are scrutinized by the scientific community. Scientists must report their findings, and communication must use standardized descriptions so that results are meaningful to any informed person to whom they are communicated. For example, in the Engage Activity of this module, students discover that imprecise or nonstandard units of measure applied to a description of a peanut greatly diminish the ability of that description to help another person to identify the same peanut. Scientific communications are subjected to peer review in journals and meetings, and the award of research grants also requires assessment by other scientists. In addition, the division of labor in scientific research provides further opportunities for critique of research and for the development of multiple lines of evidence and helps to build a more complete explanation. These procedural requirements contribute to the intellectual discipline and rigor of science.

> *"To punish me for my contempt for authority, Fate made me an authority myself."*
>
> Albert Einstein

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Science is not monolithic; it attempts to be authoritative, but it is not authoritarian. Certainly, recognition of an "authority" in a particular area of study encourages other scientists to pay attention to what is reported by that individual or research group, but the requirements for supporting evidence and all of the other criteria of valid science still apply. A famous name in itself does not establish disciplined methods or produce the credible evidence required to substantiate an idea presented to the scientific community. The rules of science are the same for everyone, and anyone who proposes a new explanation for a natural phenomenon ultimately must answer the same two questions from any other scientist: "Where are your data?" and "How do you know they are sound?" The establishment of valid scientific explanations depends upon review and critique by the scientific community at large, but the critique begins with the individual scientist. Scientists are trained to be critics of their own work. Indeed, the British biologist Peter Medawar noted that "most of a scientist's wounds are self-inflicted" (Pyke, 1996). In addition, at any given time, a minority view on some important scientific concept usually exists. With time, if sufficient evidence is brought to light, even an unpopular view can be validated.

5. How and why does scientific knowledge change?

- Scientific explanations always are open to change.
- New evidence may show that an existing explanation is inadequate and that it needs to change.

Most scientific explanations are reinforced by new observations. For example, Mendelian genetics remains durable because it explains an enormous number of observed phenomena. Not all aspects of inheritance are explained adequately, however. Scientists observed that, despite the power of Mendelian genetics, these explanations alone cannot explain phenomena such as variability in onset and severity of some genetic diseases (genetic anticipation). An explanation for anticipation became possible with the discovery of unstable trinucleotide repeats in mutant genes associated with disorders that exhibit anticipation, such as Huntington disease. (See Section V of the *Overview for Teachers*, page 43, for a detailed discussion.) In this process, geneticists did not reject Mendelian explanations; there was no scientific reason to do so. Mendelian explanations endured, but geneticists recognized that these explanations were incomplete, and they remedied that problem with new explanations.

Because scientific knowledge is dynamic, as genetics amply illustrates, scientists expect that explanations will be extended and refined. "Scientists rarely conclude that a question is finally answered or that a natural phenomenon is completely explained" (AAAS, 1989). The corpus of accepted scientific knowledge, however, changes only when rigorous criteria are met; it is not changed based on whim or to please important people.

Sometimes, new explanations must await new technology. For example, genetics could explain the general inheritance of Huntington disease for many years before it could explain the variability in the age of onset and severity of symptoms of this genetic disorder. With the use of molecular techniques for cloning and sequencing DNA, scientists discovered unstable trinucleotide repeats, thus providing the foundation of an explanation for genetic anticipation. Future work will pursue a more thorough explanation of the *mechanisms* through which large numbers of trinucleotide repeats in particular genes bring about genetic disorders; at present our knowledge is limited to the simple correlation of the presence of repeats and the disorders.

> *"The domain of ignorance includes all the things we know we don't know; all the things we don't know we don't know; and all the things we think we know but don't."*
>
> Ann Kerwin

6. What is the difference between pseudoscience and science?

- Pseudoscience fails to meet the intellectually rigorous requirements of science.
- Internal consistency sets scientific knowledge apart from pseudoscience.

Pseudoscience can be defined as the promotion of unsubstantiated, allegedly scientific opinions. Some

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of these opinions may be very appealing and thus they gain popularity, but they lack supporting, credible evidence. Pseudoscientific ideas have not been tested reliably. Often, pseudoscientific ideas are built on inaccurate premises, or they do not follow logically from what is observable. Indeed, pseudoscience could describe concepts that might be accurate, but the lack of scientific method in the pseudoscientific assertions prevents us from being able to determine the validity of the ideas being adduced. Pseudoscience often involves claims for which it is almost impossible to provide scientific evidence. Just as a poorly formulated hypothesis cannot easily be tested, pseudoscientific claims usually are so vague, ill-formed, and undetailed that they make no specific predictions and cannot be tested through credible experiments.

Pseudoscientists are those who refuse to adhere to scientific standards—they do not try to rule out competing explanations, they do not subject their results to the scrutiny of the scientific community, they do not rely on publicly observable data, and they do not test their hypotheses against scientific results elsewhere. Often, ideas based in pseudoscience are inconsistent with other well-tested concepts. Indeed, pseudoscientific claims may not be internally consistent. Without rigorous criteria for evidence and reasoning, proponents of pseudoscience are not likely to recognize these inconsistencies. We may find ourselves drawn toward the ideas put forth by pseudoscientists because they have an emotional appeal, but, when we do so, often it is because we are being intellectually lazy. Science is not easy, but it does provide sound results. New scientific findings sometimes challenge comforting, long-standing assumptions about the natural world, but scientists must go where the data take them even if the destination is a bit unsettling. Many of the characteristics that establish the overarching nature of science are summarized in Figure 8.

The Student's View of Scientific Methods

Too often students see science as either a collection of facts to be memorized or as a set of experiments, by which students mean manipulations of chemicals and glassware in a laboratory. Students may not recognize the rigorous thinking skills that go into the careful observation, the reasoned explanation, or the design and interpretation of experiments as essential elements in the practice of science. It is possible to have students experience these and other elements of scientific investigation by making the thought processes as evident and important as the processes

Figure 8 Some characteristics of the nature of science

Scientific explanations are rooted in causal processes.	Scientific knowledge is durable but dynamic.	A historical view of science shows similarities between biology and other fields of study.
Science provides explanations for natural phenomena. Causal processes are often complex and thus cannot be summarized in simple, universal laws. Scientific explanations are based on evidence. Multiple lines of evidence strengthen an explanation. A scientific explanation is a continuum of understanding that expands as new evidence for causal processes comes to light. Different levels of evidence exist and thus provide different levels of confidence in an explanation.	As new evidence appears, scientific explanations are modified; explanatory power generally increases through this process. New work builds on old work. Science (at its best) is neither monolithic nor authoritarian. Science is open to new ideas, including ideas initially expressed by a minority of scientists. Scientists expect that explanations will be extended and refined.	Because science is a human endeavor, it reflects human behaviors and limitations in human abilities. The views expressed in the other columns of this figure are true for science as a whole, but they may not apply consistently to each individual scientist. Not all good science must be experimental ("bench") science; observational studies often provide powerful lines of evidence and alter scientific explanations. This especially is the case for historical sciences such as paleontology.

of physical manipulation. The following discussion elaborates four simple components of scientific investigation (see Figure 9). Students may benefit from your calling attention to these steps. As you do so, however, you should point out that these components do not always—perhaps not even most of the time—occur in the sequence indicated. The process is much more fluid than a simple listing of steps conveys, and a scientist may be engaged in any or all of these steps at the same time. In fact, most scientists probably do not proceed consciously through these steps. It is, rather, their training and the requirements of scientific validity that lead them to incorporate all of these steps at some point as they pursue answers to a particular question. The important point for students, then, is not that research follows some prescribed, lock-step process, but rather that all research embraces the same habits of mind.

Careful and precise observation, coupled with accurate reporting, is a powerful scientific tool. Observations involve descriptions of events as they occur in the natural world or as the outcome of experiments. Observations in science must be as accurate and reliable as possible. Precision in instrumentation is crucial; technology that malfunctions (for example, a faulty DNA sequencing machine or a bug in computer software) can lead to inaccurate observations. Reliable observations are those that are reported by more than one observer and that are, in principle, replicable by any future observer. Reports that cannot be replicated at present have limited reliability, even though they could be replicated at some point in the future. Until that occurs, such reports should play only a very limited role in scientific investigation.

Figure 9 Simplified steps in the process of discovery

Define a question based on previous knowledge and rigorous observation.

Propose a potential explanation (a hypothesis). This explanation must take into account what is already known, and it must be testable.

Test the explanation. If evidence supports it, the explanation gains validity. If evidence does not support the explanation, the explanation must be abandoned and a new one sought.

Test new evidence against existing explanations. If credible evidence shows that existing explanations are inadequate, they must be modified. The new explanations must meet scientific criteria, and they will require repeated testing to establish their predictive power.

Observations must be done carefully to minimize the effect of extraneous factors. One must report observations with precision. An example from Activity 3 illustrates these points. If a student reports that a particular person has a copy of the gene associated with Huntington disease containing trinucleotide repeats, or even that the gene has many trinucleotide repeats, the information is insufficient to indicate whether the symptoms of Huntington disease likely will result. It is more precise and more meaningful to note that the gene has "more than 40 trinucleotide repeats," because about 40 copies of the CAG repeat represent a threshold level that leaves the region very unstable and generally results in Huntington disease. It is even more precise to report the exact number of CAG repeats, such as 95, thus supplying the data one needs to predict more accurately the age of onset of symptoms for the person in question.

Careful observations can be the source by which a scientist's attention is called to a particular problem or unexplained phenomenon. After recognizing a problem or puzzle, a scientist must formulate a testable question (hypothesis). Often the question is a smaller part of the overall puzzle. Testing the hypothesis comes next, and testing requires additional careful observations and reporting. The proposed explanation generally describes a causal process. As scientists pursue explanations for natural phenomena, they also must take into account existing or durable knowledge. Students often are surprised to learn that the first place to find an explanation or the answer to a question is the library, not the laboratory. Because reinventing the wheel is not a good use of research time and funds, scientists look for adequate explanations in the existing, durable knowledge that already has met the rigorous criteria of scientific validity.

The study of Huntington disease offers an example of the importance of scientific literature as part of the discovery process. Scientists investigating Huntington disease read reports that a molecular mechanism had been found to explain genetic anticipation

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(variability in age of onset and in severity of symptoms) for another autosomal dominant disorder, myotonic dystrophy. Sequencing the mutant myotonic dystrophy gene revealed an expansion in the number of trinucleotide repeats from one generation of affected individuals to their more severely affected offspring. This observation led investigators to look for unstable trinucleotide repeats in the mutant Huntington disease gene. They tested the chromosomes of individuals known to have Huntington disease and confirmed the phenomenon of expanded repeats. Note that the establishment of causality for genetic anticipation occurred in stages. Scientists first established that anticipation occurs and subsequently identified unstable trinucleotide repeats as the generalized cause of anticipation. Students model this sequential process of discovery in the procedural steps of Activity 3. The next step for scientists is to determine *how* this phenomenon of unstable repeats brings about the related genetic disorder. In Activity 3, you can help students see that pieces of the puzzle still are missing.

Activity 2 addresses extranuclear inheritance in the form of mitochondrial inheritance. In this activity, students initially may select a hypothesis from among traditional inheritance patterns to explain the pattern in two pedigrees that show mitochondrial inheritance. Students must test their hypothesis, using statistics; they flip a coin to model the likelihood that a given trait will occur according to the inheritance pattern they have chosen. The failure of their hypothesis to predict the observed outcome with any significant degree of accuracy will suggest that the hypothesis of a traditional inheritance pattern is not adequate. Students then must seek a new explanation outside the durable and traditional patterns of inheritance. This process of discovery leads the students to build a nontraditional explanation of inheritance—mitochondrial transmission—to account for the inheritance pattern they observe in the puzzling pedigrees.

The development of a new explanation usually does not negate existing knowledge. More often, new explanations extend existing scientific knowledge. The discovery of DNA and RNA as genetic material that houses the genetic code did not refute the observation that chromosomes are the location of genes; rather, the molecular data brought a more detailed and refined view of the gene. Development of a new explanation requires much more than imagination. New ideas need to connect conceptually to existing knowledge, and they must be supported by a sufficiently large body of evidence to make them convincing. Sometimes it is readily apparent that existing knowledge cannot explain the phenomenon in question. For example, Mendelian genetics assumes that genes are stable, and it explains Huntington disease on the basis of autosomal dominant transmission. Substantial evidence from family pedigrees and, more recently, from direct analysis of DNA supports this explanation. Mendelian genetics, however, has no explanation for variation in age of onset and severity of Huntington disease. As a consequence, geneticists defined a new problem: What characteristic in the mutant Huntington disease gene causes this variability?

Summary

Disciplined scientific investigation is designed to produce ever better explanations for how things work in the natural world. There are, however, limitations to this process that are worth emphasizing for students. This process does not, for example, lead to absolute truth, where "absolute" means final and complete; scientific explanations always are open to change. The foregoing review of genetic anticipation showed that Mendelian genetics is not the final explanation for transmission of genetic disorders. Although scientists have added a new chapter about trinucleotide repeats, this chapter remains incomplete because we do not know how the number of repeats increases nor do we know how the repeats influence basic cellular processes. We are therefore helpless to alter the outcome other than to choose not to reproduce. Thus, genetic explanations, like all scientific explanations, are open-ended. This does not mean that open-ended explanations are false or poorly supported or worthless. Open-ended explanations that result from scientific investigation in all cases have greater intellectual weight and authority than proposed explanations that have not been subjected to the requirements of scientific investigation. Scientific explanations may be incomplete, but it is not true that anything goes. This is an important point for your students.

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Because science, at its best, produces powerful explanations that always are open to critical analysis and revision—even if only in the direction of greater precision—scientists themselves must be open to the work of others. It is for this reason that science is a public activity; it is not the private province of any one scientist. As a result of the collective nature of science, scientists expect other scientists will review and test their work. As a further result, science proceeds necessarily along multiple, and often complementary, lines of investigation, as we saw with the cross-fertilization of research on Huntington disease and research on myotonic dystrophy. This collective nature of science helps avoid bias and reduces subjectivity, and it imposes on all scientists the intellectual discipline that comes with being accountable to other scientists.

Genetics also offers a look at the cultural and historical context of science. The rediscovery of Mendel's work 35 years after its publication demonstrates the importance of precise communication in science and the role of a cultural context that is ready to accept new knowledge. The examples of nontraditional inheritance included in this module are not the first examples of extensions of Mendel's explanations; even genetic linkage was a new twist on Mendel's ideas made possible by the observation of chromosome behavior.

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Section IV
ELSI: Ethical, Legal, and Social Implications of Nontraditional Inheritance

Genetic knowledge and technology raise numerous ethical, legal, and social issues, and the U.S. Congress has mandated approximately three percent of the annual budget for the Human Genome Project (HGP) to support research, discussion, and public education about the social implications of the human genome research. The goals of the Ethical, Legal, and Social Implications (ELSI) program of the HGP are as follows:

- to anticipate and address the ethical, legal, and social implications for individuals and society of mapping and sequencing the human genome;
- to stimulate public discussion of the issues; and
- to develop policy options to ensure that the information is used for the benefit of individuals and society.

The activities in this module address all three goals, and Activity 4 particularly emphasizes these ideas through ethical and policy questions raised by genetic testing in conjunction with new genetics concepts. Research, including that supported by the Human Genome Project, continues to uncover new mechanisms of inheritance, and with these discoveries will come additional ELSI concerns.

A central concept in this module is that new genetic knowledge has led to a rethinking of the concept of the gene. In classical Mendelian genetics, the gene is seen as a physically stable entity. The traditional concept assumes that the gene does not change during transmission, nor does it move from a fixed place within the genome. Nontraditional inheritance extends the concept of the gene to a much more flexible unit of information. Genes are sometimes unstable, in terms of location and of sequence. One example of instability is the expansion or contraction of the number of nucleotides in a given gene. Another example involves genetic elements, called transposons, that can move within the genome. Scientists did not predict these changes as they constructed the concept of the gene, a process that began with Mendel and resumed in earnest in the early decades of the twentieth century following the rediscovery of his work. The central ELSI question in this module is: **How does our changing concept of the gene and inheritance raise ethical, legal, and social implications for individuals, communities, and society?**

This module focuses on ELSI topics that have not received a great deal of attention in the literature. These topics merit consideration in this module particularly because they concern the nature and methods of science. For instance, questions of interest here include:

- What is the nature (and value) of genetic knowledge produced by the HGP and related genetics research?

- How does society perceive and use that knowledge?
- How does society influence research?

Other topics of interest focus on ethical issues associated with the HGP, particularly the knowledge that no one is free from the risk of genetically related health problems. One topic of particular concern for students is the question of how to evaluate scientific explanations, including scientific reports in the lay press. Finally, ethical issues involve prudential judgments about the clinical application of genetic information and the decision-making capacity of teenagers with respect to such information.

Developing new concepts of the gene, genetic health, and genetic disease

A basic concept in genetics is that phenotype is a function of genotype and environmental influences. For example, your potential height at adulthood has a genetically determined upper limit, but a variety of environmental factors such as nutrition and general health help to determine to what extent you reach that potential. To different degrees, genotype and environment account for the observed variations in human traits, including the human conditions that we call "health," "disease," "deformity," "disorder," "sickness," "normal," or "abnormal." Health generally refers to conditions that permit useful ranges of function or activity; while normal is a quality based on statistical concepts and refers to a condition relative to the majority of other humans. In addition, the term normal can reflect societal values.

We humans value certain species-typical functions that we regard as states of "health." Having genes that contribute to valued ranges of function can be characterized as genetic health, with the proviso that the expression of such genes depends on environmental factors. Conditions labeled "disease" fall outside valued ranges of function; in cases where there is a genetic basis for these conditions, they are usually termed "genetic disorders." We disvalue the results of these statistically abnormal functions if they hinder or prevent activity, comfort, or survival. Please note that students in general biology courses often encounter a misleading view of genetics because of the widespread use of examples involving single gene disorders. Students may think of the action of genes solely in terms of mutations and disorders, overlooking the fact that the vast majority of genes function well; if they did not, we would not be here. For this reason, we de-emphasize the term "affected" in the review of traditional inheritance patterns at the start of Activity 2 and refer instead to the presence or absence of a trait, which may or may not be a genetic disorder.

Humans may consider anatomic structure or physiological functions to be of diminished value on a number of grounds, including: aesthetic (for example, polydactyly); instrumental, that is, conditions that do not allow us to achieve our goals (for example, dementia); and survival (for example, cystic fibrosis). Having genes that contribute to disvalued ranges of function can be characterized as genetic disease. Sometimes, as in the case of Huntington disease, environment does not play a significant role in the development of a disorder. For that reason, single-gene disorders such as Huntington disease, PKU, Tay-Sachs disease, or cystic fibrosis will be expressed regardless of the natural environment. The same observation applies to some polygenic disorders, such as congenital heart disease or cleft lip and palate. In some diseases in which genetics plays a role, such as cancer and predisposition to heart disease, environmental factors significantly influence phenotype.

It is worth reminding students that some *statistically* abnormal traits are not labeled as such because we do not disvalue them. Valued and unusual traits include having superior intelligence, being very tall, or being able to run very fast. Thus, perception of genetic health and disease depends on values and statistical concepts, not just the latter. In the classroom, a discussion of values in this context must proceed with tact, particularly considering the likelihood that a student or family member has a disvalued genetic condition. Students need to see that it is the *trait*, and not the *individual*, that has diminished value.

In Mendelian genetics, genetic health and disease are defined in terms of whether an individual has an inherited malfunction that is disvalued. Some scholars have noted an oversimplified application of Mendelian genetics with respect to human health and disease. When oversimplified, genetic health

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and disease are "either/or" phenomena: an individual either has the phenotype in question (for instance, Tay-Sachs disease) or does not have it. Even classic, single-gene disorders, however, show variation in expression, so this dichotomous view of genetics is not very accurate or helpful. Nontraditional inheritance provides an opportunity to expand our explanations of complex and nuanced concepts of genetic health and disease that will continue to evolve. For example, an understanding of trinucleotide repeat expansion provides information about the variable age of onset and severity of symptoms of genetic disorders that exhibit anticipation. Recognition of variability often is excluded from the more simple concept of genetic health and disease drawn from Mendelian genetics. Variability can be a function of penetrance, the proportion of individuals with a given genotype who exhibit *any* of the phenotypic features of the related trait. Variability also can be a function of variable expressivity, the range of phenotypic effects in individuals with a given genotype (see *Overview for Teachers*, page 37, and the introduction to Activity 3 for more information on penetrance and variable expressivity). Keep in mind, however, that human perceptions of genetic health and disease are not equivalent to the evolutionary advantage or disadvantage of specific traits. For instance, the selective advantage (partial resistance to the malarial parasite) of heterozygosity for the sickle-cell trait is present regardless of whether the individual or society recognizes it.

New concepts of genes, health, and disease also require recognition that some individuals carry genes that may result in their developing a genetic disorder, even if they do not yet manifest any symptoms of the disorder. Breast cancer is a case in point. A young woman who has the *BRCA1* gene has an 80 percent life-time risk of breast cancer, even though she may be symptom-free at present. Should we view this asymptomatic woman as diseased because we know the *BRCA1* gene likely will make her sick at some point? The classification of asymptomatic individuals challenges us to revise our traditional understanding of health and disease from a concept of polar opposites to a view of endpoints on a complex continuum.

An important implication of the Human Genome Project is that we likely will discover that each of us has genetic risk factors for one or another disorder. In other words, we need to confront the fact that no one is free of genetically based risk for disease and disability. Genetic health is, therefore, a relative term. A perception of health does not support genetic perfection, and we should discard a concept of genetic health that aims to eliminate *all* risk factors. Put another way, the concept of genetic health will have to include the presence of risk factors for at least some genetic diseases. The more serious the disease or the higher the risk, the lower the genetic health.

Students may find the idea of risk factors to be a challenging concept. The difficulty results because, at this point in the history of genetics, there is no consensus on the concepts of genetic health and disease that addresses these challenges. You may want to take the occasion, if time permits, to discuss with students the challenge of formulating scientifically sound concepts of health and disease. For example, you might ask, "Given an individual who has a large number of trinucleotide repeats and who will not develop symptoms until later in life, at what point do we consider that individual to be diseased?" The answers will depend on the point at which anatomy and physiology are statistically abnormal, on which values students think are relevant to assessing the individual's condition, and on whether students can defend the relevance and application of those values.

The social setting for science

Science has a social aspect, seen in the need for communication and collaboration among scientists and in the reciprocal influences between science and society. There is, however, a distinction between the idea that science is culturally "conditioned" and the claim that science is culturally "constructed."[1] This distinction is very important. The former view, which is consistent with the material presented in this module, holds that scientific explanations describe fundamental processes and causal relationships that are

[1] The claim that science is culturally constructed is made by some individuals who are known as postmodernists or deconstructionists.

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grounded in natural phenomena. As such, scientific explanations have predictive power. Engineers, physicians, and technicians can manipulate natural phenomena using the knowledge gained from science. Because scientific knowledge is constructed according to rigorous criteria, it should, for the most part, withstand the fads and popular beliefs of any particular society at any point in history. Yet the path by which scientific discovery proceeds is certainly conditioned by history and culture. Social and political values do help to shape science, particularly the agenda of research at any given time, because modern scientific research often requires large amounts of money. Those values also shape the ways in which we apply scientific knowledge. Examples include decisions about genetic testing, which reflect our values about autonomy and privacy, and decisions about the preservation of global biodiversity, which reflect our values about obligations to future generations.

To assert that the practice and application of science reflect social and cultural values is different, however, from asserting that those values are so influential that they render the methods of science ineffectual. This situation would make it nearly impossible to know, with certainty, anything about the natural world. This idea is an extreme representation of the view that science is culturally constructed, but it could suggest that any explanation for a natural phenomenon is valid, even if it has no scientifically reliable, evidentiary basis. The material presented in this module contradicts this extreme view, proposing instead that the rigorous discipline of scientific methods limits the effects of cultural influences on the validity of scientific explanations. Physicist A. Sokal states, "The laws of nature...are not social constructions; the universe existed long before we did. Our theories about the laws of nature are social constructions. The goal of science is for the latter to approximate as closely as possible the former" (unpublished letter to the *New York Times*, 22 May 1996).

There also is a danger in allowing students and the general public to think that debates about scientific knowledge are conducted in a manner similar to that applied to political issues, by popular vote. Science is built through intellectually disciplined consensus, but not through the consensus of voting. Scientific consensus occurs when a sufficient segment of the scientific community, having followed rigorous scientific methods, is convinced by evidence and well-reasoned argument to accept an idea. To "vote" in science would ignore the intellectual discipline of scientific methods, for example, the role of evidence in scientific investigation. (The patient awaiting an appendectomy may hope that the surgeon's knowledge of anatomy is well founded in evidence and is closely aligned with reality and not the result of whim or popular views alone.) We encourage you to help students see the difference in these views; Activity 5 provides some classroom applications.

Scientific knowledge is established as a result of scientists testing their methods and their results against the criticisms of their colleagues, a process that shows the collective nature of most scientific research. Students probably will experience difficulty in learning how to step back from their ideas so that they will not take personally conscientious critiques by other students. Your task as teacher is to insist that such critiques are never personal—what is called the *ad hominem* fallacy in logic—and that the critique always is directed to the idea expressed in what was said, and not to the student who said it. Students whose ideas are criticized should be asked, "How would you respond to the criticism of your idea?" In this way, students are taught that critiques should focus on ideas, and that ideas, once expressed, become public property for careful assessment. Participating in such disciplined discourse prepares students to be responsible citizens. Although critiques of new ideas can establish their scientific validity, society's response to new scientific knowledge will depend on society's values.

Ethical and Policy Implications

The ELSI program has led to the identification and discussion of many important ethical, legal, and social implications of the Human Genome Project. These include privacy and confidentiality of genetic information, uses and misuses of genetics in the past and their relevance to current situations, prevention of discrimination in employment and insurance, and the intrusion of genetic information into reproductive decision-making. The first two modules developed by BSCS—*Mapping and Sequencing the Human Genome: Science, Ethics, and Public Policy*

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and *The Human Genome Project: Biology, Computers, and Policy*—address a number of these issues. The student activities in this module raise ethical and policy issues about access by teenagers to genetic testing and information about themselves. You can organize student discussion of these issues effectively around two major concepts: prudential decision-making and developmental autonomy of teenagers.

In Activity 4, *Should Teenagers Be Tested for the Mutant HD Gene?*, students will encounter the present policy of not testing asymptomatic minors who are at risk for Huntington disease. The justification for this policy is as follows. First, it may be harmful to give parents (or their child) the news of a genetic diagnosis for which there is no medical treatment at present. To provide such information could adversely affect how parents raise their child, and it may be cruel to inform a child that he or she has an untreatable disorder. Second, in all likelihood, even with a high number of CAG repeats, the onset of Huntington disease will occur after the child has reached legal majority, that is, the age of eighteen. Testing will be available at that time, and the individual, who then will be a legal adult, can decide whether to be tested. Third, before the age of majority, children, including teenagers, do not possess the autonomy of adults and so should not be regarded as having a right to the information or the ability to handle that information in a competent, adult fashion.

The first two justifications involve prudential judgments, a way to make reliable, well-reasoned decisions under conditions of uncertainty. The third justification involves developmental autonomy, particularly the decision-making capacity of teenagers in the context of access to genetic information.

The first two justifications concern avoiding unnecessary risk when it is uncertain that the event actually will occur. For example, the first justification assumes that most children and most parents will react very badly to the news of a diagnosis of a disorder for which there is no treatment. The second justification buttresses this consideration by pointing out that it is unnecessary to give parents of at-risk children genetic information that will have no significance until the child reaches adulthood. Prudential judgments are the tools that we use to manage uncertainty, always a feature of genetic information because our knowledge of genetics is incomplete. In addition, we use prudential judgments to make decisions about an uncertain future, when our or someone else's future interests are at risk in ways that are to some degree unknown (in Huntington disease, as to likelihood of occurrence) but whose negative value is known (for example, causing someone to despair or become depressed). Prudential judgments are not linear, but nuanced and complex. Prudential judgments balance the perceived likelihood of the occurrence of an event against its known disvalue. In simple terms, how bad is the outcome and how likely is it to occur? When the issues are weighed, different outcomes are possible, depending on one's estimate of the incidence of occurrence and how much one disvalues the risk. Such estimates should be based on scientific information and challenged in reasoned public discourse. Students should appreciate this variability if asked to justify these two aspects of their judgment. Thus, prudential judgments enable one to deal with the ethical issues raised by the activity.

The third justification involves developmental autonomy. Students likely will resist the proposition that, just because they are not yet eighteen, they cannot make decisions for themselves. Remind students that the legal age of majority is based on a rough sense of when most people should be treated like adults and on the need for a very simple legal criterion. Age meets the latter test very readily; one has only to look at someone's driver's license to determine the number of years since that individual was born. The problem, of course, is that some people have adult decision-making capacity before legal majority, some acquire that capacity long after reaching legal majority, and some never attain it. This problem raises the need for a definition of decision-making capacity. Recent work in bioethics has developed an account of this capacity, shown in Figure 10.

Notice that there is no age requirement in this description of autonomous decision-making. In the medical care of adolescents having various kinds of cancer, most physicians are willing to regard a teenaged patient as an adult in the management of the cancer if the teenager can display the six skills listed above. Many teenagers can and do display these skills. In some cases, the young person has grown up with the disease and can take adult responsibility for its management.

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Figure 10 Skills in capacity for decision-making

1. An individual can learn and recall information about the topic at hand.
2. An individual can reason from present events to their likely future effects; that is, an individual displays the ability to reason causally.
3. An individual has and can use values to assess the worth of those likely future effects.
4. An individual can express a preference based on the first three skills and, if asked, can give an acceptable account of how he or she arrived at the preference.
5. An individual can carry out his or her preference.
6. An individual is prepared to live with the effects of his or her preference in his or her own life and in others' lives; that is, one is prepared to be accountable to others, even in situations in which one injures others' interests.

It is a fact that teenagers sometimes display difficulty with skill 2 because they have not gained sufficient mastery of causal reasoning. With respect to skill 3, their values may be unstable because they still are developing their identities and plans for the future. With respect to skill 5, some may be unwilling to accept genetic testing. With respect to skill 6, they may be unwilling to assume responsibility for the consequences of their decisions for themselves and others. Learning that one has the gene for a disorder at any age involves implications for others, for example, siblings or cousins who may be at risk, friendships that may be altered or even broken, and parents who frequently take on the burden of caregiving for their children when they become chronically ill in their late 20s or 30s. The latter complication is illustrated in the case of another chronic illness, AIDS. Many young adults with AIDS-related diseases have returned to their parents' homes for care and support. Students should be encouraged to take seriously these limitations on the developmental autonomy of teenagers and to show convincingly why these limitations do not apply in their own case. Unlike adults, who may face few burdens of proof about their decision-making capacity, teenagers must demonstrate their capacity, especially when the stakes are high. The situation described in Activity 4 is such an example, in which a teenager may learn that she or he has a fatal, nontreatable genetic disorder.

Skill 6 raises a challenge beyond the problem of the decision-making capacity of teenagers. If one learns as a result of genetic testing that one has a mutant HD gene with more than 50 trinucleotide repeats, then one's offspring will be at greater risk for developing Huntington disease than if this gene has a lower number of repeats. In the former case, the gene is likely to expand to larger sizes in future generations of offspring who inherit the gene. In ethics, concern for the well-being of one's offspring is called "obligations to future generations." This term also is used in the literature of environmental ethics to refer to our obligations to those not yet born, regardless of whether they are one's own offspring.

There are a number of conceptual issues concerning obligations to future generations. First, to whom are you obligated in the future? If you contribute to an individual's genes, then you are one of the causes of that outcome. Normally, in ethics, each of us is responsible for the events that we cause as a result of present decisions and actions. Knowing that one has a gene for an autosomal dominant genetic disorder, and procreating in light of that knowledge, makes one accountable if one's children get the gene and develop the disorder.

Second, how far into the future are you obligated? This matter becomes difficult because the transmission of an autosomal dominant genetic disorder to one's grandchildren and beyond is not entirely a function of one's own decisions; these results follow from the decisions of others (for example, affected members of the family). The issue, therefore, becomes the extent to which one has an ethical obligation to attempt to influence the choices of others. There is little consensus on this complex ethical issue because the scholarly literature on this topic is just now developing. Students should be encouraged to think through this issue together, attempting to identify lines of argument that are well supported by scientific information and by criteria for ethical argument.

Third, suppose that an individual has been tested and found to have a mutant HD gene that contains 40 CAG repeats, a number at the threshold for instability. On transmission to children, this number of repeats is likely to expand, particularly if the parent in question is male. What is the individual's obligation to children who, if they are affected, likely will

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have an earlier and more severe form of the disorder? This question is an issue of the ethical significance of genetic anticipation in determining our obligations to future generations. The dilemma involves the degree to which we should disvalue diseases in their more severe forms. It seems obvious that we should. Students can consider how the qualitative dimensions of genetic disorders should be included in our concepts of genetic health and disease and evaluated in our determination of our obligations to future generations.

The fourth issue also is controversial. Is there an obligation to avoid having children who will have an autosomal dominant genetic disorder? A relatively new biomedical technology, pre-implantation diagnosis, allows couples at risk to use *in vitro* fertilization to produce embryos and then test these embryos genetically when they reach the morula stage *in vitro*. Embryos found to have the gene for Huntington disease can be discarded, and the embryo transferred to the woman's uterus will be free of the mutant gene.

Summary

Changing concepts of the gene, a central theme of the student activities, requires us to rethink concepts of genetic health and disease. In addition to "either/or" issues of whether an individual has the gene for a disease, there are now issues of the variable of age of onset and severity of disease to be taken into account, as well as phenomena such as imprinting and uniparental disomy (see *Overview for Teachers*, Section V). As the Human Genome Project and other lines of research continue to expand our understanding of inheritance, we must confront the fact that no one is free of genetically based risk. Genetic health and disease thus come to be viewed as the endpoints of a complex continuum.

The social setting for science concerns the cultural and historical conditioning of genetic knowledge. Students need to develop some comfort with the idea that at any one moment scientific knowledge is a function of its history to date. As a consequence, scientific knowledge is durable but not necessarily adequate to explain all our future observations. Scientific knowledge is incomplete in principle; it is never certain and final. Science requires constant critique of new and existing information; this requirement means that science is a self-correcting enterprise.

Ethical issues in the student activities concern prudential judgments and developmental autonomy. Prudential judgments require students to begin with the best information that science offers and then weigh the value and disvalue of future, but uncertain, consequences. Students must become comfortable with the idea that uncertainty—which even the most rigorous science cannot eliminate completely—can be managed in an intellectually serious manner.

We have defined developmental autonomy by six discrete but related skills that one can observe in individuals. Based on this definition, a person who can demonstrate those skills should be accorded the right (moral if not legal) to make personal decisions about access to genetic testing. Unlike adults, for whom the law and ethics assume such capacity, students must become comfortable with the idea that, as teenagers, they face the burden of proof for being accorded such a right.

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Section V: Genetics: Basic Concepts and Nontraditional Inheritance

"To be humane, we must ever be ready to pronounce that wise, ingenious and modest statement, 'I do not know.'"

Galileo

This teaching module uses examples of nontraditional inheritance to illustrate the nature and methods of science. By "nontraditional" we mean modes of inheritance that are not fully explained by Mendel's laws and the classic understanding of genetics that scientists have constructed in the years since Mendel. It is not, however, the actual *methods* of inheritance that are nontraditional; rather, it is that our initial *understanding* of inheritance did not encompass these processes. This section of the *Overview for Teachers* reviews classic concepts in genetics that are a prerequisite for using this module. These concepts typically are taught in an introductory biology course. This section also describes more unusual types of inheritance. Two of the latter, mitochondrial inheritance (extranuclear inheritance) and expansion of trinucleotide repeats (related to genetic anticipation), serve as examples in the *Classroom Activities*.

As reflected in the opening genetics activity of the module, Activity 1, *Standing on the Shoulders of Giants*, modern genetics is being built on a foundation of discovery that spans more than a hundred years. Figure 11, *Milestones in the Understanding of Inheritance*, provides a snapshot of the history of genetics through a chronological account of some of the major concepts of inheritance that have been developed during the past 150 years. The dates are much less important than the intellectual history, that is, the connections between ideas and discoveries. These milestones demonstrate the durability of most genetics concepts, and they suggest the dependence of discoveries on pre-existing knowledge and on technology available at the time of the discovery. The conclusions reported here were supported by evidence derived from observation and or experimentation. For the most recent years, we have selected a few of the vast number of discoveries now being published. One criterion was to choose work that marks the first of a series of discoveries. Many human genes related to complex diseases such as cancer are being identified as part of the HGP, and biologists are beginning to understand the genetic basis of complex traits, including certain behaviors. Activity 1 uses a small set of milestone explanations to challenge students to think about how our understanding of genetics has been constructed. Students examine the relationship between ideas without, we hope, undo concern about dates or exact chronology.

Figure 11 Milestones in the understanding of inheritance

1865	Mendel proposed laws of inheritance based on his experiments with garden pea plants and was largely ignored.
1883	Roux proposed that filaments (later named "chromosomes") in the nucleus are the bearers of hereditary factors.
1883	van Beneden studied meiosis in a round worm and showed that gametes contain half as many chromosomes as somatic cells and that the somatic number of chromosomes is reestablished at fertilization.
1890	Altmann discovered what later were called mitochondria.
1900	Mendel's work was independently rediscovered by Correns, de Vries, and von Tschermak, who also did experiments in plant breeding.
1901	de Vries adopted the term "mutation" to describe alterations in the hereditary material by studying primroses.
1902	McClung argued from observations in insects that sex is determined at the time of fertilization and is dependent upon the sex determinant acquired.
1902-1909	Bateson introduced the terms "genetics," "homozygote," "heterozygote," "F1," and "F2."
1903	Sutton and Boveri independently correlated Mendel's theory of independent assortment with the behavior of chromosomes during meiosis and proposed what came to be known as the "chromosome theory of heredity."
1906	Bateson, Saunders, and Punnett reported the first case of linkage (in the sweet pea).
1909	Janssens suggested that exchanges between chromosomes occur during crossing over in meiosis.
1909	Johannsen realized the distinction between the appearance of an organism and its genetic constitution, and invented the terms "phenotype" and "genotype" to describe these. He also coined the word "gene."
1911	Morgan proposed that three fruit-fly genes are linked on the X chromosome, strongly supporting the chromosome theory of heredity.
1911	Greenfield observed "anticipation" in myotonic dystrophy pedigrees by noticing cataracts in the earlier generations of these families. Many argued that anticipation was an artifact because of bias in finding parent-child pairs.
1914	Bridges discovered a rare meiotic error in fruit flies and thus associated a specific gene with a specific chromosome. This discovery established the chromosome theory of heredity.
1915	J.B.S. Haldane, Sprunt, and N.M. Haldane described the first example of linkage in vertebrates (mice).
1927	Muller induced mutations by exposing fruit flies to X rays.
1931	Stern and, independently, Creighton and McClintock provided cytological proof of crossing over during meiosis.
1933	Morgan received a Nobel Prize for his development of the theory of the gene based on his work on fruit flies.
1944	Avery, MacLeod, and McCarty transformed the phenotype of pneumococcus and proposed that DNA (not protein) is the hereditary chemical.
1950	McClintock discovered transposable genetic elements in maize and initially was ignored.
1952	Hershey and Chase showed that phage DNA enters the bacterial cell on infection, but that most phage protein remains outside.
1953	Watson and Crick proposed a chemical structure for DNA.
1956	Tjio and Levan demonstrated that humans have 46 chromosomes.
1959	Chavremont, Chavremont-Comhaire, and Baeckeland demonstrated that mitochondria have DNA.
1961	Crick, Barnett, Brenner, and Watts-Tobin showed that the genetic language is made up of three-letter words. Nirenberg, Matthaei, Ochoa, and Khorana worked out the DNA code for each amino acid.

1962	Watson, Crick, and Wilkins received Nobel Prizes for their studies on the structure of DNA.
1968	Holley, Khorana, and Nirenberg received Nobel Prizes for discoveries concerning interpretation of the genetic code and its function in protein synthesis.
1974	Hutchison, Newbold, Potter, and Edgell demonstrated the maternal inheritance of mitochondrial DNA in horse-donkey hybrids.
1980	Engel proposed the concept of "uniparental disomy," where both chromosomes of a pair are inherited from the same parent.
1981	A group of scientists worked out the complete nucleotide sequence of the human mitochondrial genome.
1983	McClintock received a Nobel Prize for her discovery of transposable genetic elements.
1983	Gusella, et al. found a DNA marker on chromosome 4 that lay close to the Huntington disease gene. Genetic testing based on linkage analysis became possible.
1983	Rastan and Cattanarch used the term "imprinting" with reference to X chromosome behavior.
1984	Pohlman, Federoff, and Messing determined the nucleotide sequence of a maize transposable genetic element.
1986	Surani used the term "genomic imprinting" to describe the differential expression of maternal or paternal genetic material located on autosomes.
1988	Spence, et al. documented a case of cystic fibrosis caused by uniparental disomy.
1990	Blum, Bakalara, and Simpson described RNA editing in trypanosomes.
1991	Expanding trinucleotide repeats were found to play a role in fragile X syndrome and Kennedy disease.
1992	An unstable trinucleotide repeat region was found in the myotonic dystrophy gene, and a correlation between the size of the repeat region and the severity of the disease was demonstrated, thus explaining the molecular basis of anticipation.
1993	The Huntington Disease Collaborative Group discovered the Huntington disease gene and found that it contains an unstable trinucleotide repeat that is the basis of the mutation.
1994	Miki and co-workers announced the identification of a human gene, *BRCA1*, that influences susceptibility to breast and ovarian cancer.
1995	Fleischmann and co-workers published the first complete DNA sequence of a free-living organism, the bacterium *Haemophilus influenzae*, as part of the HGP.
1996	Brown and co-workers identified a gene in mice, the *fosB* gene, that is required for an essential behavior, nurturing their young.
1996	More than 600 scientists worked together to complete the sequencing of a eukaryotic species, yeast (*Saccharomyces cerevisiae*).

Traditional Concepts in Genetics

Our modern understanding of inheritance is constructed around an ever-growing collection of fundamental concepts. Figure 12 lists the traditional concepts of inheritance on which this module builds. A student of genetics generally encounters at one time the entire array of basic ideas that explain what we know of inheritance. In contrast, researchers in genetics have had to build this picture one concept at a time, without the advantage of seeing beyond the currently available evidence. These concepts are discussed here with emphasis on their historical development.

Alleles segregate. Although Gregor Mendel, working in the 1850s and 1860s, did not know about genes or chromosomes, he deduced many of their fundamental characteristics and functions from his studies of traits in peas. (See Figure 1-1 in Activity 1 for a portrait

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Figure 12 Traditional concepts of inheritance

- Alleles segregate (Mendel's law of segregation).
- Non-alleles assort independently (Mendel's law of independent assortment) except when loci are linked.
- Traits can show a dominant or recessive pattern of inheritance.
- Genotype gives rise to phenotype.
- Chromosomes carry hereditary information.
- DNA is the informational component of chromosomes. Rare events (mutations) can change this information.
- Inheritance is nuclear and vertical (from parent to offspring).
- The genetic contribution from each parent is equal (in sexually reproducing species).
- Genes are the units of inheritance and are the source of heritable biological variation.
- Genes occur at fixed locations (loci) distributed along chromosomes.
- During meiosis, chromosomes can exchange genetic material through a process called crossing over.
- Genes on the same chromosome are "linked." The closer they are, the lower is the chance that they will separate during crossing over.
- The laws of probability help to explain patterns of inheritance.

of Mendel.) Mendel's first law (the law of segregation) states that the two alleles of a gene separate from each other during the formation of gametes so that a gamete carries one allele or the other, but not both. Progeny are then produced by the random combination of gametes from the two parents. The sophistication of Mendel's reasoning is remarkable given the sparse information he had available. E. van Beneden's later studies of meiosis (see the 1883 entry for van Beneden in Figure 11) showed that gametes contain half as many chromosomes (the haploid number) as do somatic cells, and that the diploid number of chromosomes is reestablished at fertilization. This work provided further evidence for Mendel's hypotheses. In 1904, Lucien Cuenot studied coat color in mice and found that a gene can have more than two alleles. Any given individual, however, has only two of those alleles, one on each of the homologous chromosomes where the gene in question resides.

Non-alleles assort independently, except when loci are linked. Mendel's second law, the law of independent assortment, concerns the inheritance of two or more traits. The law states that the genes for different traits behave independently in the production of gametes so long as those genes are on different chromosomes. Mendel found, for example, that the determination of color in his pea plants—yellow or green—was independent of the determination of shape—smooth or wrinkled. Independent studies by Walter S. Sutton and Theodor Boveri in 1903 correlated the behavior of chromosomes during meiosis with both of Mendel's laws of inheritance. They recognized a resemblance between the separation of homologous chromosomes at meiosis and Mendel's proposed separation of trait determinants at gamete formation (the law of segregation). They also suggested that chromosomes act independently in their movement during meiosis, which would explain Mendel's law of independent assortment. A gamete receives paternally and maternally derived chromosomes; thus one trait can be inherited from the mother while another comes from the father. Independent assortment increases genetic variation by creating new combinations of alleles in gametes.

Traits can show a dominant or recessive pattern of inheritance. Mendel deduced from his pea studies that the trait determined by one allele masked the expression of its partner because he did not observe phenotypes that were a mixture of the traits determined by the two different alleles of a gene. Many inherited human traits, including disorders such as Huntington disease (dominant) and cystic fibrosis (recessive), display dominant or recessive inheritance. In your teaching, take care to distinguish between the inheritance of a *gene* and a *trait*. It is not genes themselves that are dominant or recessive, nor the way genes are inherited. Instead, it is the inheritance pattern of a *trait* that is either dominant or recessive. In other words, the effect of genes on phenotype follows a dominant or recessive pattern. Furthermore, different mutations in the same gene can have different patterns of inheritance. For example, the disorder osteogenesis imperfecta exhibits dominant inheritance as a result of certain mutations and displays recessive inheritance as a result of different mutations in the same gene (Scriver, et al., 1995, *The Metabolic and Molecular Bases of Inherited Disease*, Chapters 1 and 134).

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As Lucien Cuenot showed in 1904, a gene can have more than two alleles, even though a diploid organism normally can possess only two of those alleles. Not all genes have alleles that show a clearly dominant or recessive pattern of inheritance. In multiple allelic systems, the pattern of inheritance can vary according to the particular combination of alleles in the organism. For instance, a particular allele might result in dominant inheritance in combination with one partner but recessive inheritance if paired with another allele. Some alleles result in codominant inheritance, meaning that heterozygotes display a mixture of the phenotypes that would be present in the two different homozygous conditions. A good example is the human ABO blood antigen system, where A and B alleles can be expressed simultaneously. An individual who has two copies (doses) of the same alleles for a given trait is said to be homozygous for that trait. An individual with different alleles for a given trait is said to be heterozygous. William Bateson introduced those labels in the first decade of the twentieth century.

Genotype gives rise to phenotype. In many ways, this concept is the most basic view of inheritance. The "genotype" is the genetic composition of an organism, which, at its finest level of detail, means the sequence of nucleotides in the DNA. The "phenotype" comprises the physical characteristics of an organism, including internal characteristics that require special detection methods to be observed. The terms genotype and phenotype were invented by Wilhelm L. Johannsen in 1909 when he realized the distinction between the appearance of an organism and its genetic constitution. Phenotype results from a combination of genotypic and environmental influences. The contribution of environmental influences varies for different traits.

There are several examples of single genes whose expression is modified by other factors, such that the phenotypic expression of the gene is variable. The terms "penetrance" and "variable expressivity" are used to describe this phenomenon. Penetrance is the proportion of individuals with a given genotype who express *any* of the phenotypic features of the trait. Variable expressivity is the range of phenotypic effects in individuals with a given genotype. An example of a genetic disorder that displays incomplete penetrance is the dominant trait ectrodactyly; some people carrying the mutant allele do not have the deformity called "lobster claw" hand, and yet they can pass it on to their children. Myotonic dystrophy is an example of a genetic disorder that displays variable expressivity, with symptoms that range from cataracts to extreme muscle disorders and mental retardation. In this example, variable expressivity results from an unusual genetic mechanism: differences in the degree of expansion of the unstable trinucleotide repeat within the mutant gene for myotonic dystrophy. Penetrance and variable expressivity depend on a variety of factors including environmental influences, the action of other genes, or chance. These phenomena continually cloud our ability to make exact predictions about the likely outcomes of particular genotypes.

Counterbalancing these effects is the knowledge that, for certain disorders, a particular genotype goes a long way towards predicting an ultimate outcome. For example, someone who inherits both alleles for Tay-Sachs disease will die of that disorder sometime in childhood. In Huntington disease, a greater number of trinucleotide repeats makes it more likely that the affected person will show signs and symptoms of the disorder earlier in life. Unfortunately, at present, it is not possible to determine exactly when symptoms will first appear, or the rate at which the disorder will progress.

Chromosomes carry hereditary information. As early as 1883, biologists proposed that chromosomes carry genetic information. Wilhelm Roux proposed this hypothesis after observing filaments within the nucleus that stained with basic dyes. In 1888, W. Waldeyer gave these filaments the name "chromosomes," for "colored bodies," because the chromosomes stained very darkly. The first experimental evidence that there is a constant and regular association between chromosomes and observable characteristics of the organism came from C.E. McClung's work in grasshoppers. He suggested in 1902 that the presence of a distinctive chromosome (the X chromosome) is related to sex determination because females have two copies of this chromosome and males have only one.

DNA is the informational component of chromosomes. Chromosomes in eukaryotes are composed of

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DNA and associated proteins. Prokaryotic chromosomes generally consist of a single molecule of DNA. In 1939, E. Knapp and H. Schreiber obtained preliminary evidence that the DNA component of chromosomes is responsible for the transmission of genetic information when they correlated mutations to ultraviolet light. They noticed that the wavelength of ultraviolet light that most effectively generated mutations in the sperm of a type of liverwort corresponded to the absorption spectrum of DNA. In 1944, Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty provided more conclusive evidence by transforming the phenotype of pneumococcus bacteria with a purified substance that they showed to be DNA. In 1952, Alfred D. Hershey and Martha Chase showed that the DNA component of bacteriophage viruses entered the host bacterial cell, whereas the protein component remained outside the cell and was not involved in viral infection of the bacterium. These discoveries suggested that DNA might be the carrier of hereditary information in higher organisms as well.

In 1953, James D. Watson and Francis H.C. Crick proposed a structure for the DNA molecule, which has since been confirmed by electron microscopy. Watson and Crick's proposed double helical structure with complementary strands was based on several lines of evidence that had accumulated during the few years prior to their proposal. (The icon used to denote the titles in the Overview and classroom activities depicts this structure.) Erwin Chargraff noticed in 1950 that the amounts of adenine and thymine in DNA are equal, as are the amounts of cytosine and guanine. The proportions of the two pairs varied widely between species, however. This observation, together with the X-ray crystallographic studies by the research group of Maurice H. F. Wilkins and by Rosalind E. Franklin and R. G. Gosling, led Watson and Crick to propose their structural model. The significance of the structure of DNA is that it provides a mechanism adequate to explain the storage and transmission of genetic information.

Because DNA is the molecule responsible for the transmission of genetic information, then it follows that changes in DNA structure (mutations) can result in altered characteristics of an organism. Mutation is an essential feature of heredity because it increases genetic variation, the raw material of evolution.

Inheritance is nuclear and vertical (from parent to offspring). Mendel's laws of inheritance provided a large piece of the answer to the age-old question, "Why do offspring resemble their parents?" His laws are based on the principle that heritable factors (the genotype) that influence characteristics (the phenotype) are passed from parent to progeny in a random but mathematically explainable manner. Genetic information is encoded in the sequence of nucleotides in DNA. Prokaryotic cells (bacteria) have one large DNA molecule and, in many cases, several small circles of DNA known as plasmids. In eukaryotic cells, DNA is the major informational component of thread-like structures called chromosomes, which are found in the nucleus. Because chromosomes are observable by light microscopy, their connection to inheritance was recognized earlier than was that of DNA. These observations, coupled with the phenomena discussed in the next two paragraphs, support and help to explain Mendel's observations, and they account for the predominant patterns of inheritance.

The genetic contribution from each parent is equal (in sexually reproducing species). In 1883, E. van Beneden showed that meiosis produces gametes that have half the number of chromosomes (haploid number, N) of that found in somatic cells (diploid number, 2N) of the same organism. This reduction in chromosome number, from 2N to N, is essential for gametes to function in sexual reproduction. Without the reduction, each generation would double the number of chromosomes and hence double the genetic information.

T. H. Montgomery studied spermatogenesis in various species of *Hemiptera* (true bugs) and concluded in 1901 that maternal chromosomes pair only with paternal chromosomes during meiosis. In studying sea urchin embryos in 1903, Theodor Boveri found that this organism needs a full set of chromosomes to develop normally and deduced that individual chromosomes carry different essential elements. This observation led him to conclude not only that meiosis reduces the number of chromosomes by half, but that meiosis specifically halves *each pair* of chromosomes. Therefore, it follows that the combination of two gametes in fertilization produces a zygote that has an equal genetic contribution from each parent.

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Genes are the units of inheritance and are the source of heritable biological variation. The view of the gene is constantly evolving, as described in Petter Portin's review (Portin, 1993). First conceived as an abstract unit of inheritance, the gene now is seen as a complex molecular entity whose properties are becoming known. A gene is a portion of DNA that encodes information needed for the production of a functional product. This product is either a protein or a functional RNA, such as a ribosomal component. Protein is produced by the translation of an intermediate molecule, mRNA. Features of a typical eukaryotic gene, illustrated in Figure 13, include the coding region (the part that determines the final protein sequence) and various control regions that determine when, where, and how much of the gene product is made. The coding region may contain noncoding inserts called introns, which are excised during RNA processing. The portions of the coding region that correspond to the final version of the RNA message (mRNA) are called exons. The initial RNA product contains copies of exons and introns, but the mRNA has been processed to remove introns prior to translation.

There are about 80,000 genes in the complete human genetic endowment (the genome), but these account for less than five percent of the total DNA content (see For Your Information: *How many genes do humans have?*). Scientists do not clearly know the significance of the remainder of the DNA at this time. There may exist slightly different forms of a particular gene—a function of slight variations in base sequences—and more than one version can be present in a diploid organism. These different forms (alleles) lead to variation in the expression of traits among individuals within a species.

There are many differences in the DNA sequence between individuals, most of which make no difference to the phenotype. Some variations within genes, however, can have biological consequences. Some genetic variations lead to harmless phenotypic differences such as variations in hair and eye color, whereas others can have more serious consequences, either advantageous or disadvantageous. A DNA variation that causes a gene product to be altered or deficient in some way can manifest itself as a genetic disorder such as cystic fibrosis. These heritable changes in the DNA sequence result from mutations in germline cells. (Some mutations occur in somatic cells and are *not* heritable, as August Weissman demonstrated in the late 1800s. Germ cells are separated from somatic cells. Weissman's work helped to disprove Lamarckian's notions about the inheritance of acquired characteristics.)

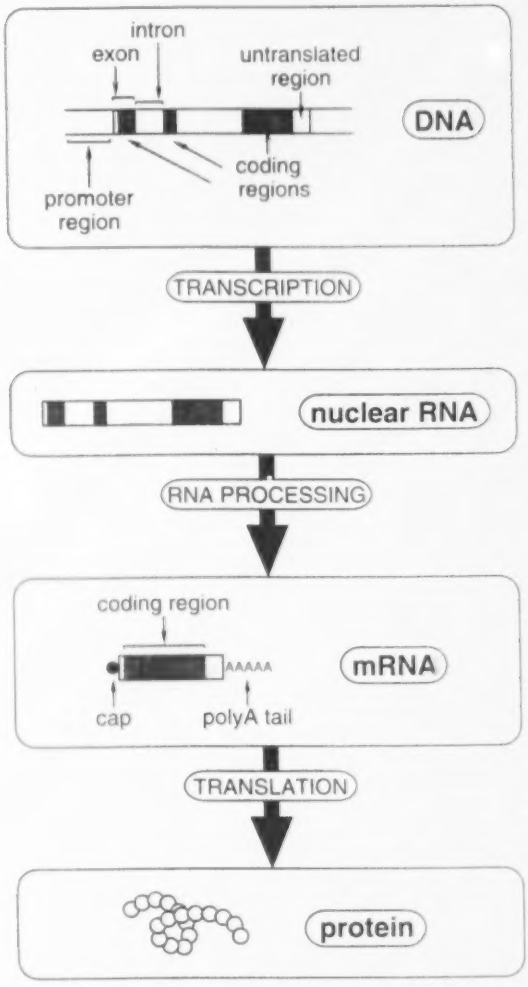

Figure 13 Features of a gene: Notice that the mRNA, when fully processed, may be shorter than the gene from which it was copied. In addition to removal of introns, processing involves two chemical modifications, a "cap" structure and a polyA tail, that are required for stability and translation.

Heritable genetic variation is an essential prerequisite to biological evolution in that it provides the

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For Your Information

How many genes do humans have?

Estimates of the number of genes in the human genome have varied over the years. Scientists have tried several approaches to determine the precise number, including estimating the number of proteins expressed in a particular cell type, estimating the number of different RNA molecules produced, and estimating the density of genes on chromosomes by looking at the DNA sequence. All of these approaches have severe limitations. For example, not all genes are expressed in any one cell type; some gene products are not proteins; variable RNA splicing allows the same gene to produce different mRNAs; and the density of genes on chromosomes varies. The sequence-based approach is the most accurate method for determining where a given gene begins and ends, and, once the Human Genome Project has achieved its goal of sequencing the entire genome, we will have a better estimate of the number of human genes. Note that it may not be possible to tell from the DNA sequence whether a gene actually is functional. As more of the genome is sequenced, the predicted number of genes is decreasing, perhaps because the regions first examined happened to be particularly gene-rich. One recent estimate is that the human genome contains approximately 80,000 genes.

array of random but transmissable changes on which natural selective pressure acts. Changes in genes give rise to differences in phenotype, and some of these may be selected for or against in the struggle to leave viable offspring that constitutes Darwinian fitness. The great evolutionary biologist Ernst Mayr reminds us that natural selection is a two-step process. The first step is the production of new genetic and phenotypic variations in a population of organisms. The second step is selection itself, which tests those variations against the environment. Gradually, the collection of genes in a species shifts, an example of the process of evolution at work. Consider the situation at the level of proteins. For some proteins, such as histones, sequence and, consequently, structure are highly conserved. We infer that the function of these proteins remains essentially unchanged, and that almost any change (mutation) is a disadvantage for the organism. Other proteins, however, are much more tolerant of variation, and more differences accumulate in the genes that encode them.

Genes occur at fixed locations (loci) distributed along chromosomes. Implicit in the classic view of inheritance is the assumption that a gene remains in a fixed location on its chromosome, with the noted exception of recombination during meiosis. Even in that case, the relative position of a gene compared to the location of its neighbors is generally fixed (see next discussion). Mendel's observations and the other principles of genetics described here are based largely on this assumption.

During meiosis, chromosomes can exchange genetic material through a process called crossing over. Crossing over of chromosomes during meiosis was first observed in 1909, when F.A. Janssens suggested that exchanges between nonsister (paternal and maternal) chromatids produced chiasmata (cross-shaped junction points). In 1931, Curt Stern obtained cytological evidence of crossing over, an observation confirmed independently by H.B. Creighton and Barbara McClintock in the same year. J.H. Taylor provided the most convincing evidence in 1965—by radioisotope labeling of grasshopper chromosomes—that there is an exchange of DNA at chiasmata. Crossing over results in genetic recombination and the production of novel combinations of alleles. This recombination is one source of the intraspecific genetic variation that makes evolution possible. The unique combination of genetic information derived from two parents also provides a variety of characteristics on which natural selection acts.

Genes on the same chromosome are "linked." In 1906, William Bateson, E.R. Saunders, and Reginal C. Punnett—while studying inheritance in the

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sweet pea—discovered the first exception to Mendel's law of independent assortment. They found that purple flowers and long pollen—both dominant traits—were inherited together more often than predicted by Mendel's second law. (The laws of probability were essential for these scientists to notice that something unusual was happening; see the discussion under the next heading.) The reason for this discrepancy is that these investigators were looking at two genes on the same chromosome, whereas five of the seven traits that Mendel studied are located on different chromosomes (the other two are far apart on the same chromosome and effectively behave independently). The two sweet-pea traits were not always inherited together because they sometimes were separated by crossing over during meiosis, but they were inherited together more often than Mendel predicted because they are close together on the same chromosome. Genes that lie close together on a chromosome are said to be more closely linked than those that are farther apart. The farther apart loci are on the same chromosome, the more their behavior is independent in meiosis because of the crossing over that can occur between them.

Thomas Hunt Morgan was instrumental in developing the chromosome theory of heredity by formulating the concept of gene linkage. In 1911, he proposed that the fruit-fly genes for white eyes, yellow body, and miniature wings are linked on the X chromosome. He and his colleagues subsequently found that the number of linkage groups is equal to the haploid number of chromosomes, and that the linear arrangement of genes within the linkage group corresponds to the linear cytological structure of the chromosome. Morgan, who did so much to develop the concept of gene linkage, is immortalized in the term "centimorgan." This term is a unit of distance used in linkage maps. Two loci that are one centimorgan apart are separated by recombination an average of one in one hundred times (or one percent of the time, that is, in one gamete out of one hundred).

Substantiation of the chromosome theory of heredity came in 1914 from the work of one of Morgan's students, Calvin Bridges, who found a rare exception to the linkage of genes on the fruit-fly X chromosome. He noticed that the exceptional inheritance of the sex-linked white eye color was accompanied by similar exceptional behavior of the sex chromosomes; he proposed meiotic nondisjunction as a mechanism for this unusual inheritance. (Meiotic nondisjunction refers to the improper separation of homologues during meiotic cell division. It is responsible for some cases of the common chromosomal disorder known as Down syndrome.)

The laws of probability help to explain patterns of inheritance. In analyzing his pea-breeding experiments, Mendel was a pioneer in the use of rigorous mathematical analysis of his biological data. The numbers of the various phenotypes of his plants led him to propose that each "particulate factor" (gene) has two "alternative forms" (alleles) and that the distribution of alleles among gametes is random. In 1889, Francis Galton (a cousin of Charles Darwin) and his associate Karl Pearson demonstrated that there is a statistical association between traits shown by parents and their offspring, even when the trait shows a continuous variation such as that for height or weight. In 1909, nine years after the rediscovery of Mendel's work, Herman Nilsson-Ehle studied seed-coat color in wheat. He proposed that continuous traits are determined by multiple genes, each of which segregates according to Mendelian principles, and each of which has a small but additive effect.

Your students presumably have encountered the laws of probability in their study of Mendel's experiments. In revisiting these principles, stress that the laws of probability are applicable only when the sample number is large enough. For example, a small sample size may not display the predicted Mendelian distributions for a given gene or trait. Independent probability, another important concept, states that the outcome of one independent event does not influence the outcome of subsequent independent events. This concept often is summarized by the phrase, "probability has no memory." For instance, when considering the inheritance of an autosomal recessive disorder such as cystic fibrosis, the chance that each child of heterozygous parents will be affected is one in four; it is not correct to say that the birth of one affected child means that the next three will be unaffected. You can emphasize this point by examining the traditional pedigrees (A-H) in Activity 2, *Puzzling Pedigrees*.

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Mathematical principles also were central to the derivation and application of the Hardy-Weinberg equilibrium in population genetics. W.E. Castle, in 1903, recognized a relationship between gene and genotype frequencies. Then, in 1908, Godfrey H. Hardy and Wilhelm Weinberg independently discovered a mathematical relationship that explains the general stability of gene and genotype frequencies in a population as genes are passed from generation to generation. The Hardy-Weinberg equilibrium shows, contrary to prior assertions, that a dominant trait will not drive its recessive counterpart from a population of organisms. Equilibrium—stability in gene and genotype frequencies—is the rule, assuming the absence of evolutionary forces such as selection or genetic drift, and if there is minimal mutation.

Genetics and Evolution

No overview of classical genetics, even so brief a treatment as presented here, is complete without a discussion of the relationship between genetics and evolution, the conceptual thread that binds all of biology. Charles Darwin realized that variation among the members of any population of organisms is fuel for the fires of natural selection. In fact, Ernst Mayr asserts that one of Darwin's most important contributions was the firm establishment among biologists that a species is not composed of one fixed, identical type, but rather of unique individuals that differ from one another in a variety of ways. Furthermore, Darwin realized that the only variations that are important to natural selection and speciation are those that can be passed from generation to generation.

Darwin had a vexing problem, however: he could not define a valid mechanism by which variations could be transmitted unchanged from one generation to the next. The prevailing wisdom of the time—the late-nineteenth century—was blending inheritance, the view that the characteristics of both parents blend together in the offspring, producing progeny that are intermediate in character between the two parents. Fleeming Jenkin, an engineer, argued in the 1860s that blending inheritance would make differential selection impossible because all members of a population would be the same. Furthermore, within a few generations, blending inheritance would vitiate the effects of any new variations that arose.

Darwin, who published *The Origin of Species* in 1859, could have found substantial help in the work of his contemporary, Gregor Mendel, who published his paper "Experiments in Plant-Hybridization" in 1865. Although Mendel almost certainly was aware of Darwin's work, most historians of science agree that Darwin never read Mendel's paper, for, had he done so, he likely would have recognized that Mendel's experiments provided solutions to his nagging problem. Mendel had demonstrated the particulate nature of inheritance, showing that hereditary information is carried by some discrete elements in the germ cells. These discrete elements permit the transmission of traits in unchanged form. We now call these elements genes.

Ironically, the rediscovery of Mendel's work in 1900 (about two decades after Darwin's death) caused serious problems for Darwin's theory. As evolutionary biologist Douglas Futuyma (1986) explains, biologists of that era "dismissed continuous variation among individuals as inconsequential and largely nongenetic, and emphasized the role of discontinuous variants that displayed Mendelian ratios and clearly particulate inheritance." In 1918, however, Ronald A. Fisher found supporting evidence for Nilssan-Ehle's proposition about multiple genes. Fisher showed that continuous variation (height, for example) results from multiple genes that are inherited in Mendelian fashion and that have small, additive effects.

The growth of population genetics and its accompanying mathematical models led to the Modern Synthesis of Evolution during the 1930s and 1940s. This reconciliation of Mendel and Darwin involved some of this century's greatest biologists, among them Sewall Wright, J.B.S. Haldane, Ronald Fisher, Ernst Mayr, George Gaylord Simpson, Theodosius Dobzhansky, and G. Ledyard Stebbins.

The 1944 discovery by Avery, McCarty, and MacLeod that DNA is the genetic material and the 1953 delineation of DNA's structure by Watson and Crick provided additional opportunities to investigate genetic aspects of organic evolution, including the causes, rates, and effects of mutation. One obvious and current example of the relationship between genetics and evolutionary biology is the ability to compare

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DNA base sequences among species to help establish phylogenetic relationships.

In summary, the growth of genetics and the growth of evolution theory are intimately related. Because genetics is the study of the root source of biological variation, which is central to evolutionary mechanisms, an understanding of basic principles in genetics is central to an understanding of evolution itself.

Nontraditional Concepts in Genetics

The following sections describe some of the concepts of inheritance that have been discovered since the development of the classical understanding of inheritance in the late nineteenth and early twentieth centuries. Keep in mind that it is not the *inheritance* that is nontraditional, but rather our *understanding* of the inheritance that is new. Figure 14 lists the nontraditional concepts of inheritance described in this Overview.

Some heritable traits are extranuclear. Mendelian principles of inheritance apply to chromosomes that are found in the nucleus, but not to DNA that is located elsewhere in the cell. For instance, mitochondrial DNA is packaged into a circular chromosome, of which there are thousands of copies per cell. All of the mitochondria in a fertilized zygote are contributed by the ovum; none come from the sperm. Activity 2 introduces students to the concept of maternal inheritance of mitochondrial genes. (Copymaster 2-5 in Activity 2 includes an illustration of mitochondrial inheritance.) A similar phenomenon of extranuclear inheritance occurs in the inheritance of chloroplast DNA.

Figure 14 New (nontraditional) concepts of inheritance

- Some heritable traits are extranuclear (mitochondrial inheritance, cytoplasmic inheritance).
- Genetic anticipation (increased severity of a genetic disorder in later generations) correlates with expansion of trinucleotide repeats.
- Genomic imprinting can alter the expression of genetic information and distinguish its parental origin.
- Both chromosomes of a pair may, in rare cases, come from one parent (uniparental disomy).
- Some genes are mobile and can insert themselves in new chromosomal locations.
- Genes may, in rare cases, undergo horizontal transfer between individuals or species.
- Many traits result from expression of more than one gene combined with environmental factors (multifactorial inheritance).
- Genetic information specified by genomic sequence may be altered during RNA editing.

Genetic anticipation correlates with expansion of trinucleotide repeats. Traditional principles of genetics predict that the structure of a gene remains stable as it passes from parent to child. Even in situations where a mutation arises in a gene, the altered structure generally remains fixed and is inherited in that form. The recent discovery of unstable trinucleotide repeats, however, has shown that parts of the gene are not so stable.

The term "trinucleotide repeat" refers to a specific DNA sequence of three nucleotides that is repeated over and over again, one after the other. The precise number of these repeated trinucleotides at particular locations in the genome varies from person to person. These so-called "polymorphic" (multiple forms) repeat regions are largely stable; that is, when a particular chromosome is passed from parent to child, the number of repeated trinucleotides remains the same. The size of the repeated unit can vary from two to several hundred nucleotides. The variability and stability of these polymorphic repeat regions provide the basis of DNA fingerprinting, which is used in forensic and medical application (see For Your Information: *DNA fingerprinting*, p. 44).

Most regions of trinucleotide repeats stay the same length. Some trinucleotide repeat regions are unusual, however, in that they are unstable once they exceed a particular size. Phenotypic effects of this phenomenon are evident in cases where the unstable trinucleotide repeat region lies within the portion of a gene that is transcribed to RNA (although not necessarily in the coding region, see Figure 15).

Molecular biologists uncovered the first example of this phenomenon in 1991 with the discovery of the gene causing fragile X syndrome, an X-linked disorder that is the most common cause of inherited mental retardation (see For Your Information: *Fragile X syndrome*, p. 45). Here, research

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For Your Information

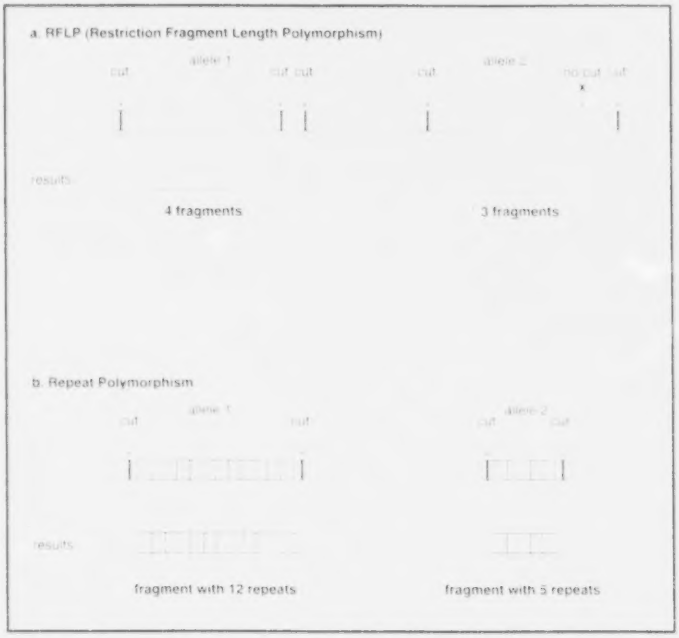
DNA fingerprinting

Some DNA differences between two individuals can be detected only by comparing nucleotide sequences. There are, however, two basic kinds of DNA variation, or polymorphism, that are detected more easily, as shown in the illustration. One of these types of polymorphism is the restriction fragment length polymorphism (RFLP)—the variable length of DNA fragments produced by the presence or absence of a recognition site for a specific restriction endonuclease.

A second type of DNA polymorphism is an array of repeated DNA sequences that varies in the number of repeated units. Not all the arrays of repeated sequences are polymorphic, but those that are serve as excellent markers for tracing the inheritance of particular regions of the genome. One of the reasons that repeat polymorphisms are more useful than RFLPs is that the number of alleles at a particular locus can be highly variable. In contrast, an RFLP usually has only two alleles (the presence or absence of restriction-endonuclease recognition site). Repeat polymorphisms are therefore very informative.

If one investigates a repeat polymorphism by Southern analysis, the location of the probe determines the nature of the result. If the probe corresponds to the repeated sequence itself, then bands representing *all* genomic locations of the polymorphism will be evident. This approach is the nature of the DNA fingerprinting method developed by Alec Jeffreys in 1985, where each DNA sample from an individual looks like a bar code. This technique can be used for forensic purposes by matching DNA from specimens at a crime scene with DNA isolated from suspects. Alternatively, DNA fingerprinting can be used to rule out or provide strong evidence for parentage, because each band in someone's "bar code" has been inherited from one or the other parent. For instance, if there are bands in a child's DNA fingerprint that do not appear in the DNA pattern either of the supposed father or the known mother, then the paternity must be questioned.

Another way to follow repeat polymorphisms is to use a probe just outside the repeat region, where the DNA sequence is unique, or to use the polymerase chain reaction (PCR) for specific isolation of the repeat region. This method can be useful in finding DNA markers linked to disease genes.



DNA polymorphisms. (a) RFLP: In allele 2, a missing recognition site for a restriction enzyme results in digestion of fewer sites and in the generation of a different pattern of fragments. **(b) Repeat Polymorphism:** The number of sequence repeats may vary between alleles. When the repeat region in each allele is cut out using a specific restriction enzyme or amplified by PCR, the number of repeats can be compared.

For Your Information

Fragile X syndrome

clinical features

The principal features of fragile X syndrome in affected males are mental retardation, long face, and large testes after puberty. Carrier females do not have a distinctive appearance, but about one-third are mildly mentally retarded.

incidence

For human males, this disorder is the most common cause of inherited mental retardation, occurring in 1:1000-2000 male births. Incidence in females is lower, around 1:8000.

inheritance

Fragile X syndrome, as the name implies, is an X-linked trait; it shows variable penetrance and expressivity. About one-fifth of males who transmit the mutant gene have no symptoms themselves. About one-third of heterozygous females show some clinical features. The likelihood that symptoms will appear in family members increases in later generations. This observation originally was called the "Sherman paradox." Because of new molecular data, the Sherman paradox now is attributed to expansion of a trinucleotide repeat region.

gene and protein

The gene responsible for fragile X syndrome lies on the X chromosome and was isolated in 1991. The gene product is a protein that has RNA-binding properties, but its precise function in the cell is still being investigated. The gene contains a polymorphic and unstable CGG trinucleotide repeat in the portion of the gene that is transcribed, although the repeat region lies outside the coding region. The normal range of variation in the trinucleotide repeat number is 5-50; beyond that, the repeat becomes unstable and can expand during transmission from parent to child. Expansion is more pronounced when an unstable allele is inherited from the mother. (The number of repeats correlates to the presence of symptoms see Figure 15).

disease mechanism

Expansion of the trinucleotide repeat in fragile X syndrome disrupts production of the protein product, which under normal circumstances is found at highest levels in the brain and testes. Lack of this protein presumably prevents normal development of these tissues in particular.

diagnosis

Diagnosis based on clinical manifestations generally occurs in infancy or early childhood. Large ears and slow development are indications. Diagnosis has been possible by cytogenetic analysis; this test uses lymphocytes and can be done at any age, including prenatally. Cytogenetic analysis relies on detection of fragility of the X chromosome characteristic of this mutation. A preferable diagnosis uses molecular genetic analysis of the associated repeats in the gene associated with fragile X mental retardation (*FMR1*).

treatment

No treatment is available for fragile X syndrome.

revealed a polymorphic CGG trinucleotide repeat that lies in the region of the gene transcribed into mRNA but outside the coding region. Studies of the fragile X gene revealed a correlation between the number of CGG repeats and the phenotype. All male patients with fragile X syndrome had more than 200 CGG repeats, whereas unaffected people from outside these families had between 5 and 50 CGG repeats. A third group of people with between 50 and 200 CGG repeats were those family members who were unaffected carriers of the disorder. Alleles with greater than 50 CGG repeats

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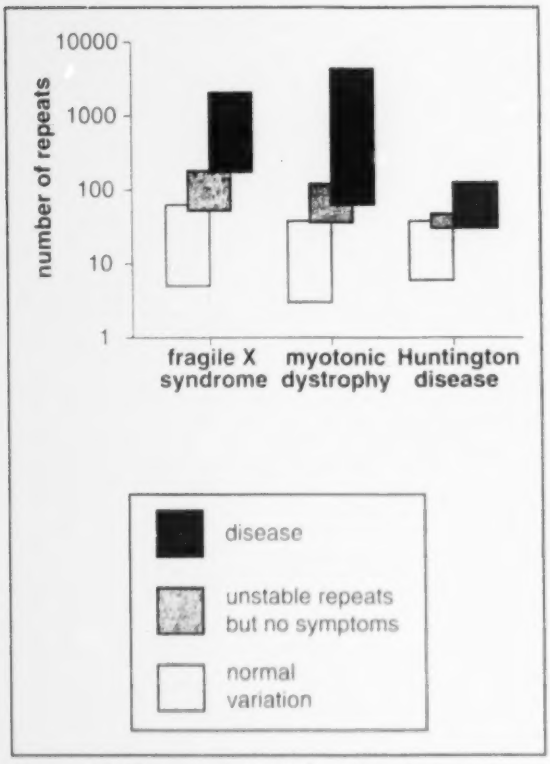
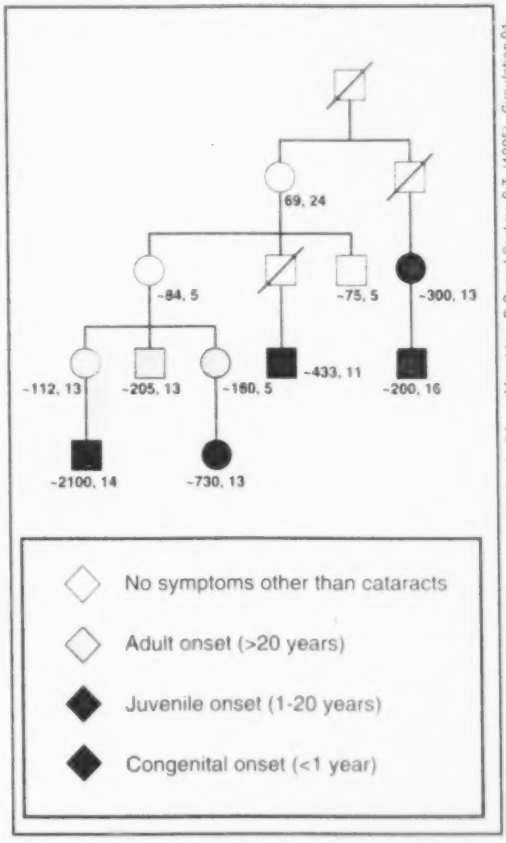


Figure 15 The number of trinucleotide repeats correlates to phenotype for certain genetic disorders: Notice the overlap of symbols, suggesting that the number of repeats is not the only factor to influence manifestation of the disorder.



"Anticipation and repeat expansion in myotonic dystrophy," from Monckton, D.G. and Caskey, C.T. (1995) *Circulation* 91 513-520. Reproduced with permission

Figure 16 Correlation between the trinucleotide repeat number and the clinical features of myotonic dystrophy: The numbers represent how many copies of the trinucleotide repeats are present in each allele.

usually increased in size during passage from parent to child, especially when the unstable allele came from the mother. Generally, the greater the number of repeats, the higher the likelihood that expansion will occur during transmission to the next generation. We do not know the precise mechanism of the instability (which is usually, but not always, expansion) and the reason for the differences in parental inheritance.

Soon after the discovery of the fragile X gene and its unstable trinucleotide repeats, biologists discovered the same type of mutation in several other disorders (Figure 15). Two of these, myotonic dystrophy and Huntington disease, serve as examples in Activity 3, *Clues and Discoveries in Science* (see For Your Information on each of these topics: *Myotonic dystrophy*, *Huntington disease* and *Predictive testing for HD*). Myotonic dystrophy and Huntington disease exhibit "anticipation," which is the increasing severity and/or earlier onset of symptoms in generations of an affected family. This phenomenon is particularly apparent in myotonic dystrophy, where there is a good correlation between the length of the unstable trinucleotide repeat and the severity of the symptoms (see Figure 16). As with fragile X syndrome, the relationship between the larger number of repeats and more severe symptoms in myotonic dystrophy is unclear. Further, as with fragile X syndrome, myotonic dystrophy and Huntington disease show increased anticipation when the passage is through a parent of one particular sex. Anticipation is greater when the passage is through mothers who have myotonic dystrophy; in the case of Hunting-

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For Your Information

Myotonic dystrophy

clinical features

The symptoms of myotonic dystrophy (DM) are extremely variable. In late onset of DM, symptoms include a hollow facial appearance accompanied by sagging facial muscles. Other symptoms include cataracts, frontal balding, heart arrhythmia, myotonia (inability to release a grip), muscle weakness, defective speech, bronchitis, and mental retardation. A severe congenital form has major muscle weakness, moderate mental retardation, and exhibits myotonia in early childhood.

incidence

DM is the most common adult muscular dystrophy, occurring at roughly 1:1,800-8,000 in European and American populations, 1:18,000 in Japan, and very rarely in Africa. Reports of incidence vary depending on the criteria used to establish that an individual is affected.

inheritance

DM is inherited as an autosomal dominant disorder that shows anticipation. Expressivity of the mutant gene varies, and penetrance can be incomplete. Congenital DM is inherited maternally.

gene and protein

The mutation has been mapped to a location on chromosome 19 (19q 13.2-13.3). The affected gene has a region of unstable trinucleotide repeats (CTG). Ranges from 50 to several thousand copies of the repeat are associated with affected individuals. The locus is referred to as *DMPK* (myotonic dystrophy protein kinase). The gene product is a protein kinase, sometimes called myotonin kinase.

disease mechanism

The exact mechanism is not understood. Symptoms develop as a result of weakness, atrophy, and myotonia of affected muscles, especially in the face and neck muscles and in the extremities. For congenital DM, the major cause of death likely is from the involvement of respiratory muscles.

diagnosis

Diagnosis of adult-onset DM is based on the presence of the clinical features described above, coupled with family history, molecular genetic data, and, possibly, evidence of myotonia based on a test by electromyography. Congenital DM is diagnosed by the presence of this disorder in the mother, seen together with reduced fetal movements, muscle weakness, respiratory difficulties, and mental retardation. DM can be diagnosed by prenatal genetic tests combined with ultrasound.

treatment

Physical therapy and surgery for cataracts are useful for mild adult symptoms. External pacemakers may help patients who have atrioventricular blocks.

ton disease, anticipation is greater through affected fathers. We do not know the mechanisms for these sex differences, but they could involve differential instability of the trinucleotide repeats during meiosis; another possible mechanism is imprinting (see the following discussion).

Several other genetic disorders are associated with unstable trinucleotide repeats. A review in the 1995 *Annual Review of Genetics* "Trinucleotide Repeat Expansion and Human Disease," by C.T. Ashley, Jr., and S.T. Warren, describes nine diseases in which expansion of trinucleotide repeats is

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For Your Information

Huntington disease

clinical features
Huntington disease (HD) produces chorea (twitching or twisting involuntary movements that occur when the affected person attempts voluntary movement) and dementia. Speech often is affected, and memory lapses may occur. HD is a late-onset disease that usually manifests itself in middle age or later, although the age of onset varies from one generation to another.

incidence
Approximately 1:10,000-20,000 for predominately Caucasian populations; 1:333,000 in Asian populations (particularly in Japan); incidence is lowest among African Black populations.

inheritance
HD is inherited as an autosomal dominant disorder that exhibits genetic anticipation.

gene and protein
The mutant gene for HD was isolated in 1993, although detection by linkage analysis was available about 10 years earlier. The gene is called *IT-15*, and it is located on chromosome 4, in the 4p16.3 region. The trinucleotide CAG is repeated a variable number of times, in tandem, in this gene. Repeat numbers in the range 40-100 are unstable and result in HD. There is evidence of incomplete penetrance for people with alleles carrying repeats in the range 36-39. The protein encoded by this gene is named huntingtin.

disease mechanism
HD is a neurological disorder, but we do not yet know the exact biochemical mechanism.

diagnosis
Diagnosis is made by the combined presence of chorea and dementia, positive family history, and or genetic test results showing more than 40 trinucleotide repeats in the associated gene.

treatment
There is no treatment to alter the progress of this disorder, although we can manage the symptoms to some degree with drugs.

known to play a role. Since that time, research has shown that another disorder, Friedreich ataxia, is associated with an unstable GAA repeat. This disorder often begins in childhood or adolescence with clumsiness involving the extremities. Generally, there is no mental deficiency, but the neurological problems progress steadily. Death generally results in the mid to late thirties. It is usually inherited as an autosomal recessive disorder, but about 10 percent of cases indicate autosomal dominant inheritance.

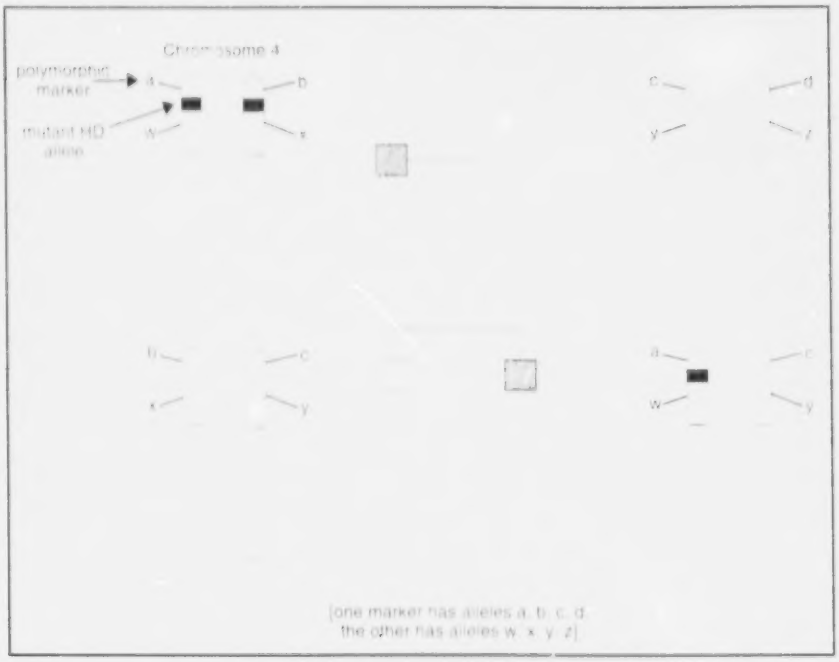
Genomic imprinting can alter the expression of genetic information and distinguish its parental origin. Mendelian principles predict that each parent contributes one copy of a particular autosomal gene to offspring. Implicit in this prediction is the assumption that the two copies of a given autosomal gene behave in the same way, such that the parental origin of a particular allele does not affect its expression. Although this assumption appears to be correct for most genes, there are exceptions. In some genes, alleles are differentially expressed, depending on their

For Your Information

Predictive testing for Huntington disease

Molecular biologists have known since 1983 that the gene responsible for Huntington disease (HD) lies near one end of human chromosome 4. At that time, the gene itself had not been found, but there was a polymorphic DNA marker whose pattern of inheritance closely matched that of HD in affected families, and which therefore was closely linked to the gene. Research soon identified additional polymorphic markers close to the HD gene, and predictive testing by linkage analysis became an option for families in 1986. Linkage analysis uses the presence of identifiable markers located quite near a gene of interest to identify the presence of that gene as being highly probable. This illustration shows predictive testing of Huntington disease by linkage analysis. The mutant gene is traveling with the "aw" haplotype.

There were a number of limitations to predictive testing by linkage analysis. Although the markers around the HD gene were linked closely, there was a 4 percent probability that they would be separated by recombination. That situation meant that if a person at risk for HD inherited the same alleles for the markers that another affected member of their family had, this person could be told with only 96 percent certainty that he or she also would develop the disease. Another problem with linkage analysis was that the polymorphic markers were not "informative" in some families. For instance, if an affected parent had identical polymorphic markers on both chromosomes, it was not possible to tell which of the chromosomes had been passed on to his or her children—the chromosome with the HD gene, or the one without the HD gene. Therefore, it was impossible to predict who in the family would develop HD. In addition, linkage analysis usually was not possible in the absence of DNA from an affected individual or other key family members.



The discovery of the mutant HD gene made direct predictive testing possible. By using Southern analysis or the polymerase chain reaction (PCR), scientists can measure the length of the trinucleotide repeat region in this gene. A person who has more than 40 trinucleotide repeats eventually will develop HD, unless death occurs by some other cause first. See Figure 15 for an indication of the range of repeat numbers seen in the HD gene.

parental source. This phenomenon is called "genomic imprinting" (Figure 17). For each imprinted gene, either the paternal or maternal allele, or both, are marked in some way that influences gene expression. It is usually the marked allele that is suppressed. We do not understand the imprinting process completely, but it gives an allele a distinctive behavior that reflects the parental source.*

A primary imprint likely is acquired at the particular genetic location during meiosis, and this imprint is maintained on the particular chromosome in the haploid gamete. After fertilization, the imprint is maintained on the paternal or maternal chromosome throughout DNA replication in the diploid zygote. That imprint then leads to functional differences between the paternal and maternal alleles in somatic cells. Imprinting is reversible in that the imprint is erased during the production of germ cells, from which gametes are derived. Imprinting may involve DNA methylation, although evidence is, at present, insufficient to establish the molecular mechanism with certainty.

Prader-Willi syndrome and Angelman syndrome illustrate genomic imprinting in humans. Prader-Willi syndrome is characterized by obesity, excessive appetite, small hands and feet, short stature, small sexual organs, and mental retardation. In contrast, Angelman syndrome is characterized by severe mental retardation, inappropriate laughter, seizures, and uncoordinated movements. The genes responsible for these disorders are in the same region of chromosome 15 (15q11-13). A tiny deletion in this region can result either in Prader-

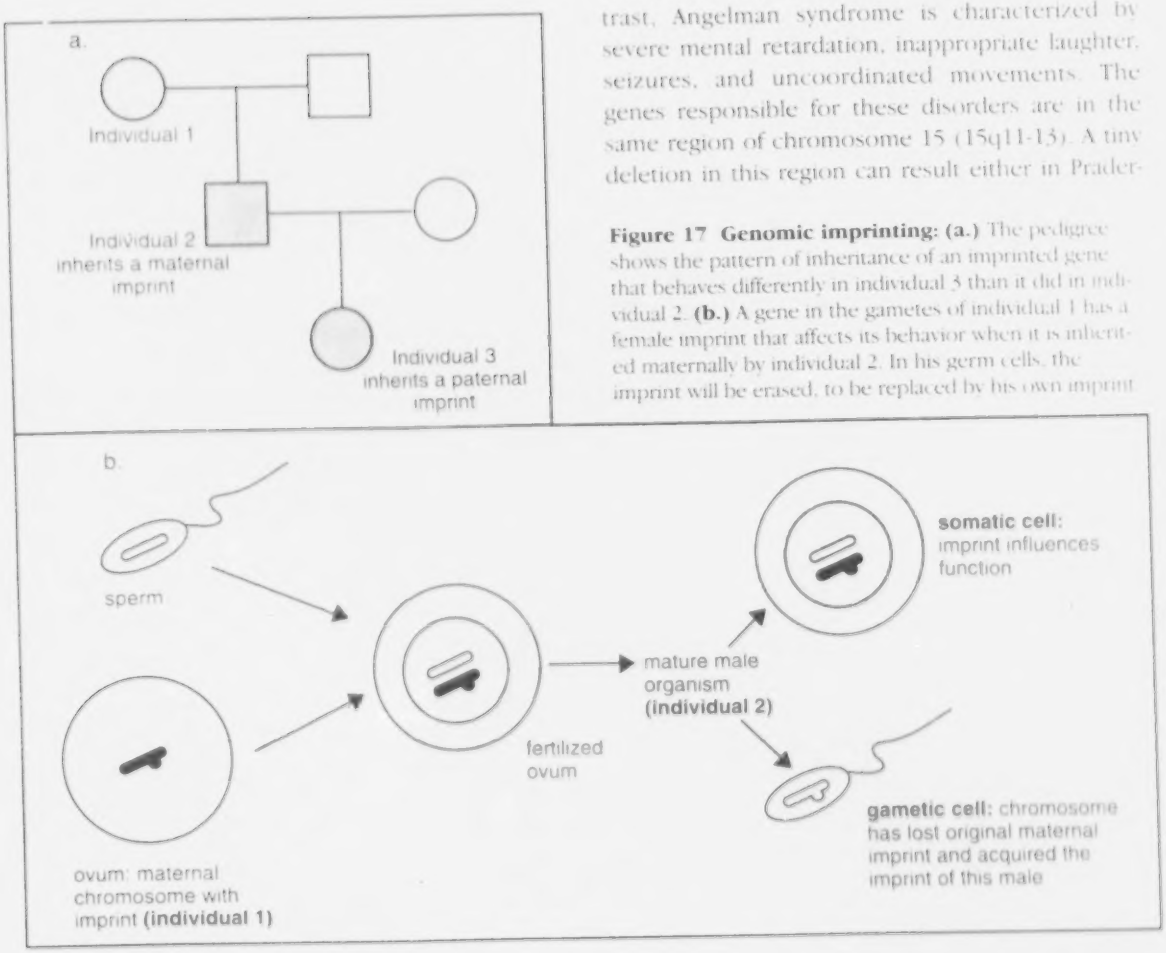

a.
Individual 1
Individual 2 inherits a maternal imprint
Individual 3 inherits a paternal imprint
b.
sperm
ovum: maternal chromosome with imprint (individual 1)
fertilized ovum
mature male organism (individual 2)
somatic cell: imprint influences function
gametic cell: chromosome has lost original maternal imprint and acquired the imprint of this male

Figure 17 Genomic imprinting: (a.) The pedigree shows the pattern of inheritance of an imprinted gene that behaves differently in individual 3 than it did in individual 2. **(b.)** A gene in the gametes of individual 1 has a female imprint that affects its behavior when it is inherited maternally by individual 2. In his germ cells, the imprint will be erased, to be replaced by his own imprint.

* The term imprinting has an interesting history. It was used earlier in a genetic context to refer to the selective elimination of a paternal chromosome or to the selective inactivation of the X chromosome derived from the male parent.

Willi syndrome or Angelman syndrome; the disorder that results depends, in part, on the parental origin of the chromosome carrying the deletion (see Figure 18). If the chromosome 15 deletion is of maternal origin, Angelman syndrome results. Prader-Willi syndrome results if the chromosome 15 deletion is paternal in origin. This difference suggests that the region containing the genes associated with these disorders normally carries an imprint that distinguishes the maternal and paternal alleles and that influences gene expression.

Additional evidence for imprinting comes from extensive studies in mice. Embryos that have a full set of chromosomes derived from only one parent invariably fail to develop properly, even though they have a complete set of genes. Without a maternal set of chromosomes, the embryo is abnormal, and without a paternal set of chromosomes, the placenta fails to develop. That phenomenon also occurs in humans. These observations suggest that the parental source of a chromosome can influence its effect; normal cells require a complement of maternal and paternal genes. It also is not possible to generate a viable embryo from the fusion of two female ova, or from the fusion of oocyte chromosomes with chromosomes from the first polar body (a by-product of meiosis).

Both chromosomes of a pair may, in rare cases, come from one parent. Mendelian principles predict that, in a pair of chromosomes, one homolog has been contributed from each parent. In rare situations, however, this pattern is not the case, and both chromosomes of a pair are inherited from the same parent. This unusual form of inheritance is called "uniparental disomy." This situation may arise from a starting condition of trisomy—the extra chromosome then is lost. If it was the only homolog from one of the parents, uniparental disomy results. If the remaining pair of chromosomes came from one parent and are *identical*, the condition is called uniparental "*iso*disomy." If the remaining pair of chromosomes came from one parent and are *different* homologs, the result is uniparental "*hetero*disomy." Errors in chromosome replication can result in these unusual patterns of inheritance.

The phenotypic consequences of uniparental disomy include the unusual inheritance of autosomal recessive traits and aberrations related to imprinting. Uniparental disomy in humans was first recognized in the late 1980s, when a girl with cystic fibrosis and short stature was found to have two identical copies of much or all of the maternal chromosome 7. Her mother was a heterozygous carrier of a cystic fibrosis allele, and the daughter maternally inherited a duplicate copy of the mutant allele, resulting in uniparental isodisomy for chromosome 7. The short stature probably resulted from an imprinting effect. This cystic fibrosis example shows one pattern that can signal uniparental disomy: a child expresses a recessive trait but, surprisingly, it is not true that *both* parents carry the recessive allele, as would be expected based on traditional concepts of recessive inheritance.

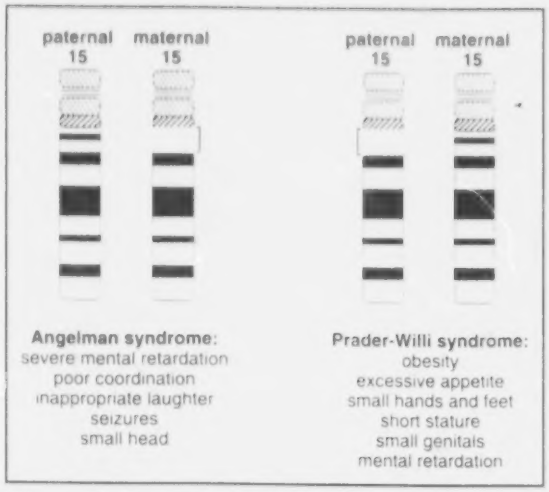


Figure 18 Genomic imprinting results in different phenotypic expression in these two human genetic disorders: Deletion in the same region of human chromosome 15 behaves differently depending on the parent of origin. Maternal inheritance results in Angelman syndrome; paternal inheritance causes Prader-Willi syndrome. Uniparental disomy can produce a similar effect.

If the chromosome pair for which there is uniparental disomy includes an imprinted gene, and if the donor parent is the one whose alleles are suppressed, then that gene will not be expressed in the offspring. That situation is one of the mechanisms by which Prader-Willi syndrome can occur, since the inheritance of two maternal chromosomes 15 has the same effect as a localized deletion in the appropriate part of the paternal chromosome 15. Prader-Willi syndrome can occur as a result of (maternal) uniparental *isodisomy* or *heterodisomy*.

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Some genes are mobile and can insert themselves in new chromosomal locations. Classic laws of inheritance assume that a gene occurs at a fixed location in the genome. There are, however, "transposable genetic elements" that are mobile. Barbara McClintock, while performing breeding experiments in maize (*Zea mays*) in the 1940s, was one of the first scientists to recognize that genes could move around in the genome. She saw odd patterns in the inheritance of pigments in maize kernels that one could not explain by conventional genetic theories. She eventually concluded that a few genes do not have fixed locations in the genome but instead move from one location to another during the passage from parent to progeny.

Barbara McClintock's discovery of transposable genetic elements is a good example of the nature and methods of science. She made observations in the 1940s that did not fit the classic understanding of inheritance, and she proposed new explanations for those observations. Although her hypotheses were not widely accepted at first, she continued her work and, gradually, with the accumulation of more evidence, her views gained strength. In the 1970s, experiments in molecular biology provided a mechanism for the behavior of transposons. Molecular data demonstrated that small pieces of DNA sometimes move around the genome, triggering changes in gene expression. McClintock's hypothesis is now widely acknowledged, and she won the Nobel Prize for Physiology or Medicine in 1983. McClintock is one among many scientists, male and female, who struggle to gain acceptance of revolutionary ideas that contradict the prevailing wisdom. Science is inherently self-correcting, so one expects that accurate explanations ultimately will prevail.

Since the original discovery of transposable genetic elements in maize, research has uncovered similar factors in other species, including bacteria, fruit flies, and humans. Transposable genetic elements are like viruses in that they can incorporate themselves into the host genome; they do not, however, have a protein coat and therefore are restricted to movement within a single cell. In moving, a transposable genetic element breaks away from its site in the genome and inserts itself somewhere else, either in the same or a different chromosome. Sometimes a copy of the element is left in the original location; other times it is excised completely. Not surprisingly, the movement of transposable genetic elements can be quite disruptive. Insertion of a transposable genetic element into a gene can turn off its expression (which is what was happening in McClintock's genes for maize pigment). Inaccurate repair of the DNA at the original site can cause a gene mutation.

Genes may, in rare cases, undergo horizontal transfer between individuals or species. Mendelian patterns of inheritance apply to the vertical transmission of genes from parent to child. Genes can be transmitted horizontally, however, as in the transfer of genes between individuals or species. The classic example of this is the demonstration that one can change the phenotype of bacteria by transferring DNA from one strain to another (see the entry for 1944 in Figure 11). Whereas gene transfer between prokaryotes is not uncommon, there is little evidence to show that it has happened in eukaryotes. Nevertheless, it is possible that a transposable genetic element called a P element was passed from one species of fruit fly to another sometime in the last 50 years. It is possible that this DNA transfer occurred through the mouthpiece of a parasitic mite. Another possibility for cross-species gene transfer is through viral vectors.

Many traits result from expression of more than one gene combined with environmental factors (multifactorial inheritance). Classic inheritance patterns are more easily recognized in traits that result from single genes than in those traits that result from more than one gene (polygenic) and that are influenced significantly by environmental factors. This combination of environmental influence and action of multiple genes is called multifactorial inheritance. These types of traits might appear to run in families, but without any recognizable pattern. Figure 19 illustrates the concept of a multifactorial trait. (Many single gene traits are subject to environmental influences. Although multiple factors are at work in such circumstances, the term multifactorial generally is reserved for polygenic traits that are influenced by environment.)

When Mendel's laws were rediscovered at the turn of the twentieth century, the factors of inheritance

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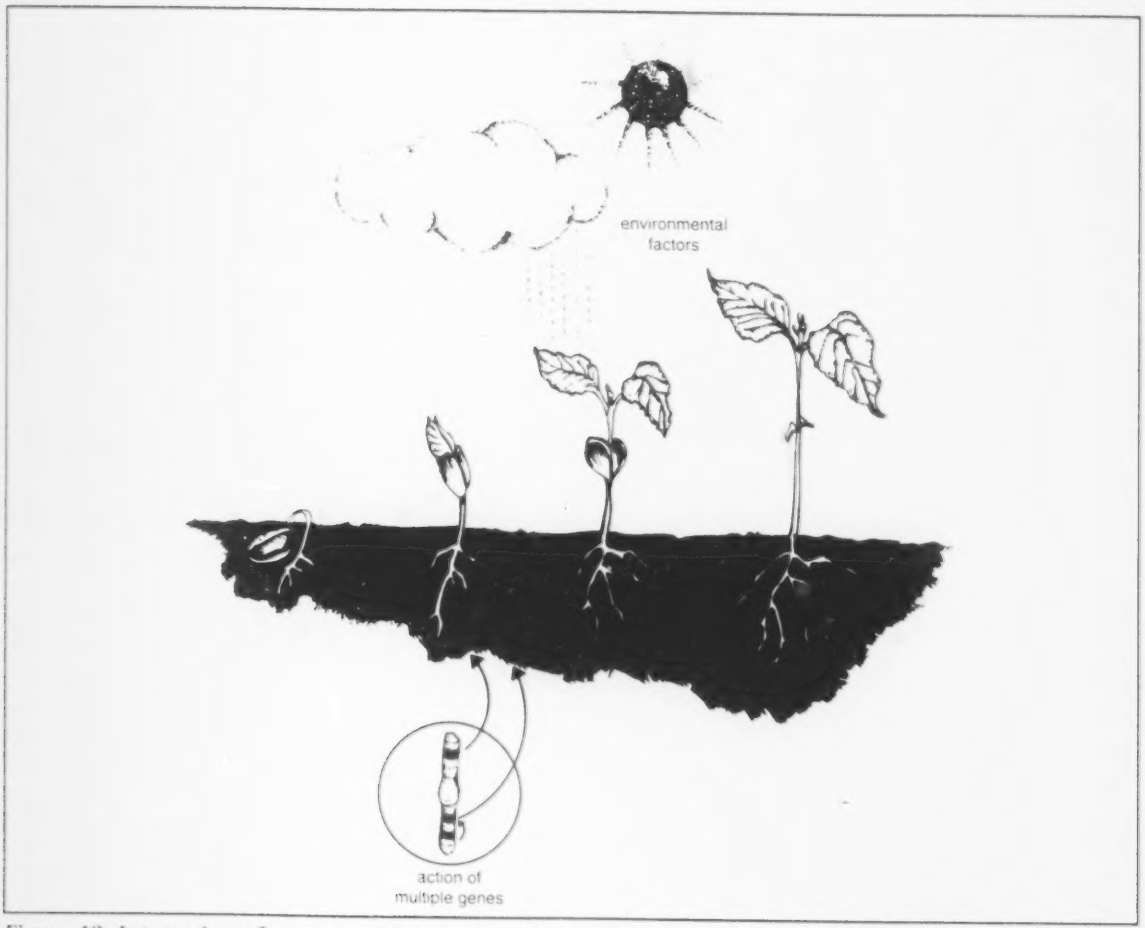

Figure 19 Interaction of genotype, phenotype, and environmental influences: Many traits result from the combined influence of several genes plus environmental factors.

were viewed as particulate and fixed so that outcomes from any given genotype would be similar, if not identical. Since that time, we have learned that a variety of factors can affect the phenotype in addition to what is prescribed by the genotype. Environment, for example, often influences genotypic expression. Plants or people that inherit genotypes for tall adult stature will show that phenotype only if placed in an environment where nutritional factors allow them to reach the potential of their genotype. If placed in a nutritionally restricted setting, no genotype will allow them to reach great stature. Similarly, we know that genes can act on each other or contribute directly to phenotype. For example, some inherited anemias may be less severe in individuals who have counterbalancing genes for the increased production of red blood cells. Finally, there is a strong element of chance in the expression of many genes, an element that is not yet well understood. Chance may play a role in the time at which a certain gene is turned on or off, which can affect the timing of the appearance or relative degree of expression of a trait.

Multifactorial traits (as distinct from single-gene traits that show variable expression) can be divided into three classes characterized by continuous variation, threshold traits, and complex adult disorders. In traits that show continuous variation, an "abnormal" phenotype simply represents an extreme variation of the normal range. Examples include many kinds of nonspecific mental retardation and unusual height (very

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short or very tall). In multifactorial threshold traits, there is a clear distinction between normal and abnormal phenotypes. In these cases, there may be an underlying continuous variation until a particular threshold is reached, at which point the abnormal phenotype appears. This model has been proposed to explain several common congenital abnormalities such as cleft lip and palate and neural tube defects (such as spina bifida). In complex adult disorders such as coronary artery disease and diabetes mellitus, there is a variety of genetic and environmental influences. Here, a person is genetically predisposed to a particular illness, but can impose a strong influence on the outcome by lifestyle choices (such as diet).

Genetic information specified by genomic sequence may be altered during RNA editing. Classic genetic principles predict that an mRNA molecule, which directs the synthesis of a protein from amino acid components, is faithfully transcribed from its parent gene. Biologists have known for about 20 years that the coding region of a eukaryotic gene is usually interrupted by introns that are excised during mRNA processing, but they assumed that the coding portion of mRNA remained unaltered during the conversion from precursor RNA to mature mRNA.

Research in recent years has uncovered a phenomenon called RNA editing, where crucial coding information is added to the mRNA after its transcription from DNA. The best understood example of RNA editing is that seen in trypanosome parasites, which cause sleeping sickness and other illnesses. In 1986, molecular biologists made the baffling observation that mRNAs from some of the mitochondrial genes are longer than the genes from which they are derived. Additional (uridine) bases had been added at specific points throughout the mRNAs, making sense of what, at the DNA level, was nonsense. Research done in 1990 proposed an explanation for this observation: smaller circles of DNA in the trypanosome mitochondria, whose function was previously unknown, produce small "guide RNAs" that find and correct omissions in the mRNA. The evolutionary significance of such a mechanism is still a mystery. Perhaps RNA editing is related to the well-known ability of the trypanosome to change its antigenic structure and thereby confound the immune response of the host organism.

Summary

This section of the *Overview for Teachers* emphasizes that our understanding of inheritance since the time of Mendel has endured and changed—and, indeed, is still changing. Traditional Mendelian genetics continues to describe accurately the majority of what we observe in inheritance, and new discoveries continue to refine and extend our level of understanding of the gene and of genetics.

For additional information on some human genetic disorders, contact the following organizations:

Alliance of Genetic Support Groups
35 Wisconsin Circle, Suite 440
Chevy Chase, MD 20815-7015
1-301-652-5553
FAX: 1-301-654-0171
E-mail: alliance@capaccess.org
http://medhlp.netusa.net/www/agsg.htm

Huntington's Disease Society of America
140 West 22nd Street, Sixth Floor
New York, NY 10011-2420
1-800-345-HDSA (4372)
1-212-242-1968
http://neuro-www2.mgh.harvard.edu/hdsa/hdsaman.nclk

The National Fragile X Foundation
1441 York Street, Suite 215
Denver, CO 80206
1-800-688-8765
1-303-333-6155

Muscular Dystrophy Association
3300 East Sunrise Drive
Tucson, AZ 85718-3208
1-602-529-2000
http://www.mdausa.org

For CompuServe users, you can use the Communication Service Forum and ask the experts online. Get into the system and type GO MDA.

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Glossary

We have provided this glossary for your convenience. The memorization of these terms is *not* an objective of this module, and we encourage you *not* to turn this list, or any portion of it, into a test.

affected: the condition of having a particular trait, usually used in the context of a disadvantageous trait, as for a disease symptom.

allele: one of the alternative forms of a gene at a given locus.

anticipation: earlier onset or increased severity of an inherited disorder in subsequent generations. (See trinucleotide repeats.)

autosome: a chromosome *other than* a sex chromosome. Humans have 22 pairs of autosomes.

chiasma: (plural is chiasmata) the point of crossing over during prophase I of meiosis in which there is an actual exchange of genetic material between the paired maternal and paternal copies of chromosomes.

coding region: a stretch of DNA sequence (in a gene) that encodes protein.

codominant: the condition in which a pair of alleles for a given locus equally contributes to the phenotype of the heterozygote who bears them.

congenital: existing from birth (note that this term does not distinguish whether the condition is inherited, or environmental, or both).

credible: (in the context of scientific methods) the condition of being reliable and based on acceptable methods, as in reference to evidence that meets scientific criteria for accuracy and reproducibility.

cytogenetics: a subdiscipline of genetics that combines the study of the cell with the study of genetics, often focusing on the structure, function, and behavior of chromosomes.

deletion: (in the context of molecular genetics) the absence of one or more nucleotides normally found in a gene, resulting in a mutation.

developmental autonomy: (in the context of ethics) having sufficient mental and emotional maturity to be capable of informed consent.

diploid: having two copies of each chromosome; a diploid cell has a chromosome number of 2N. In humans, the diploid number is 46.

DM: abbreviation for the human genetic disorder myotonic dystrophy. This disorder shows variable expressivity, with symptoms ranging from cataracts and

mild muscle weakness to extreme muscle wasting and contraction, impairment of some organ function, and mental retardation. DM displays genetic anticipation as a result of unstable trinucleotide repeats in the mutant gene associated with the disorder.

DOE: the United States Department of Energy.

dominant: the pattern of inheritance in which an allele expresses its phenotypic effect even in heterozygotes and masks that of some other allele at the same locus. A trait expressed by dominant inheritance is called a dominant trait.

ELSI: Ethical, Legal, and Social Implications, a division of the Human Genome Project.

eukaryote: an organism in which cells have a membrane-bound nucleus. Eukaryotes have other subcellular organelles, such as mitochondria or, in the case of plant cells, chloroplasts. Humans are eukaryotes.

expression: in the molecular context, the transcription of a gene into RNA products, some of which are also translated into proteins. In a larger genetic context, expression refers to the phenotypic manifestation of an allele. .

extranuclear inheritance: inheritance from DNA sources external to the chromosomes found in the nucleus. Extranuclear inheritance can derive from mitochondrial DNA or chloroplast DNA. Other terms used for this phenomenon are maternal inheritance (for mitochondrial inheritance), cytoplasmic inheritance, or extrachromosomal inheritance.

gamete: a sexual reproductive cell. Gametes are haploid, having a single (N) complement of genetic material. In humans, the gametes are ova and sperm.

gene: the basic unit of heredity, in terms of function and in the physical sense. A gene is a region of DNA that is transcribed (into RNA) plus the regulatory DNA sequences necessary for transcription. (Not all genes encode protein. For example, in the genes for ribosomal RNA, the transcript is the functional product.)

genome: the entire complement of genetic material. The Human Genome Project defines the human genome as a single haploid set of nuclear chromosomes, plus the mitochondrial genome.

genotype: the genetic make-up of a cell or organism. Genotype can be contrasted with the phenotype (the detectable attributes). Genotype also can refer to the particular allelic make-up for a given gene.

haploid: a cell (or organism) having only one chromosome set (N). (See gamete and diploid.)

HD: abbreviation for the human genetic disorder Huntington disease. HD is a disorder of the nervous system, usually with adult onset of symptoms. The disorder displays genetic anticipation as a result of unstable trinucleotide repeats in the mutant gene. The disorder is fatal.

heritable: capable of being transmitted to offspring.

heterodisomy: a particular example of uniparental disomy (q.v.) in which the two chromosomes are nonidentical homologs. (See also isodisomy.)

heterozygous: the condition of having two different alleles at a particular locus on a pair of chromosomes (homologs).

HGP: the Human Genome Project; a large, collaborative, scientific research effort funded in the United States by the U.S. Department of Energy (DOE) and the National Institutes of Health (NIH).

homolog: one of a pair of chromosomes that contain equivalent genetic information. In germline cells, homologs pair with one another during meiosis. One homolog is derived from the mother and one from the father.

homozygous: the condition of having identical alleles for a particular gene at a given locus in a chromosome pair.

hypothesis: a testable idea or explanation proposed in response to previous knowledge and specific observations.

imprinting: (in the context of genetics) a process through which a gene becomes marked chemically in a manner that reflects the sex of the parent transmitting the gene. Imprinting alters the function of a particular allele such that an allele inherited from the male parent behaves differently from an allele that is inherited from the female parent. Not all genes are imprinted. The exact mechanism for imprinting is not known.

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informatics: the study of information processing. In the field of biology, informatics generally refers to the study of genetic sequence data.

isodisomy: a particular example of uniparental disomy (q.v.) in which the two chromosomes are identical. (See also heterodisomy.)

karyotype: the entire set of chromosomes of an individual cell made visible by staining and microscopy and arranged by size and chromosome number.

linkage analysis: a laboratory technique that determines the presence of a gene of interest by the presence of identifiable markers located close to the gene.

linked genes: genes located on the same chromosome. Genes that are close together—tightly linked—are less likely to be separated during recombination.

locus: the location of a gene on a chromosome.

marker: (in the context of genetics) an identifiable allele that expresses a known phenotype or a molecular tag (such as a DNA or RNA fragment) to signal the presence of an allele or chromosomal location of interest. DNA or RNA fragments also are used to bind to, and thus identify, a particular genetic sequence in a nucleic acid fragment.

meiosis: a specialized process of cell division that reduces the chromosome number to the single (haploid) complement (N). Meiosis takes place in germline cells. Meiosis produces 4 haploid daughter cells from one diploid cell, involving one round of DNA replication.

Mendelian genetics: the fundamental concepts of genetic transmission put forward by Mendel and expanded to include knowledge of genetic linkage and sex chromosomes.

methylation: a chemical process that adds a methyl group to a molecule; this process can be carried out in living systems by enzymes called methylases. DNA can be methylated at specific sites, a process that may regulate gene expression. Methylation has been suggested as a possible mechanism of genomic imprinting. Methylation is involved in X-chromosome inactivation.

mitochondrial DNA: the DNA found in mitochondria, the organelles of eukaryotic cells that are important in energy-related reactions. Mitochondrial DNA can replicate independently of the genomic DNA found in the nucleus, and cells have many mitochondria. In humans, mitochondria are transmitted maternally.

mRNA: messenger RNA, the fully processed form of the transcript copied from the DNA sequence of a gene and used to direct protein synthesis.

multifactorial inheritance: inheritance in which the phenotype results from combined action of more than one gene (polygenes) with additional environmental influences.

mutation: a physical change in genetic material, such as a base-pair substitution or deletion in DNA. Chromosome breaks or rearrangements involve large-scale mutations. If the mutation occurs in body (somatic) cells, the results affect only the individual bearing those cells; if the mutation is in germline cells, the change can be transmitted to offspring.

nondisjunction: improper separation of homologs or sister chromatids during meiosis or mitosis. During meiosis, this process can result in a diploid condition for a particular chromosome in one gamete and the absence of that chromosome in another gamete.

nontraditional inheritance: an informal term that refers to new concepts of inheritance that describe processes that were not traditionally understood or taught in Mendelian genetics. For example, imprinting is a process not explained by traditional Mendelian concepts.

ovum: a female gamete, commonly called an "egg."

PCR: polymerase chain reaction. A laboratory technique that exploits DNA polymerases (enzymes that help replicate DNA) derived from bacteria that live at high altitudes. The technique permits the *in vitro* production of large amounts of DNA copied from a very small amount of sample DNA.

penetrance: the proportion of individuals with a given genotype who express *any* of the phenotypic features of the trait. Incomplete penetrance refers to the situation in which less than 100 percent of individuals with a given genotype express the associated phenotype.

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phenotype: the externally or internally detectable characteristics of an organism that represent the influences of environment and genetic information (the genotype).

polygenic: a condition that results from the interaction of several genes, each of which contributes a small effect to the trait in question.

polymerase chain reaction: see PCR.

polymorphic: literally, having more than one form, such as different lengths for restriction fragments of DNA, or the presence of two or more genetically distinct types in a population.

probe: (in the context of molecular genetics) a substance labeled with radioactivity or a fluorescing compound that is used to identify a gene, transcript, or protein through a binding reaction.

prokaryote: a colonial or single-celled organism whose cells lack a membrane-bound nucleus. A prokaryote has a relatively simple cell structure without organelles such as mitochondria or chloroplasts. Bacteria are prokaryotes.

prudential decision-making: the ethical term that refers to making a choice through a disciplined analysis involving well-reasoned discourse, a consideration of various aspects of an issue, and a weighing of risk.

recessive: a pattern of inheritance in which the phenotypic effects of an allele are masked in heterozygotes when one of certain other alleles is present. A trait expressed by recessive inheritance is termed a recessive trait. A recessive trait is expressed only in homozygotes.

relevant: (in the context of science) the condition of relating to or addressing a particular idea. Relevant evidence is evidence that is useful to support or contradict an explanation.

restriction endonuclease recognition site: a specific DNA sequence that is recognized and cut (digested) by specific members of a class of bacterial enzymes known as restriction enzymes. This process supplies a naturally occurring immune function for bacteria and is exploited in the laboratory to make possible cloning and other molecular techniques involving specifically sized DNA fragments.

restriction fragment length polymorphisms (RFLPs): the small differences in the length of DNA fragments produced through cutting with restriction enzymes (enzymes that cut DNA at specific sequences). Genetic variation between individuals is reflected in small differences in the length of DNA between the sites recognized by restriction enzymes, thus producing RFLPs. These differences can be exploited to map the location of genes.

ribosome: structure within cells on which protein synthesis occurs. Ribosomes are composed of ribosomal RNA (rRNA) and proteins.

somatic cell: a cell that does not produce gametes. In humans, somatic cells are all cells except the germline cells in ovaries and testes that will undergo meiosis. A mutation in a somatic cell affects the function of that cell and all body cells derived from it, but it is not passed on to offspring.

spermatogenesis: the development of sperm, a process that involves meiosis.

theory: (in the context of science) an explanation of a fundamental principle that has been so thoroughly tested and supported by multiple lines of evidence that it is accepted by the scientific community.

transcription: the process through which an RNA molecule is synthesized by complementary base pairing using DNA as a template. For example, messenger RNA (mRNA) is a product of transcription.

translation: the process of synthesizing a protein molecule. An RNA message (mRNA) directs the order of amino acids being bonded together to form a protein. This process takes place on structures known as ribosomes.

transposable genetic element: a transposon; this element is a small sequence of DNA that does not necessarily remain at a fixed locus within the chromosome. A transposon can jump to a new location, exerting its influence on genes near the new locus.

trinucleotide repeat: a specific sequence of three nucleotides (subunits of DNA) that is repeated, often in large numbers, in a continuous stretch of DNA in particular genes. The mutant gene for Huntington disease, for instance, contains the trinucleotide CAG repeated many times. When the number of repeats

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passes a threshold number (around 40 in Huntington disease) the stretch of trinucleotide repeats becomes unstable and may increase (or, rarely, decrease) between one generation and the next. Large numbers of repeats result in disease. Trinucleotide repeats are part of the biological explanation for genetic anticipation (q.v.).

uniparental disomy: a relatively rare genetic process through which both copies of a particular chromosome (both homologs) are derived from the same parent.

validity: (in the context of science) the condition of having met scientific criteria, such as being supported by credible evidence, being built on correct premises, and showing sound reasoning.

variable expressivity: the range of phenotypic effects in individuals with a given genotype. (Note that small differences in the genotype may be present but not obvious.)

X-linked trait: a pattern of inheritance in which the allele for the trait in question is present on the X chromosome. Males have only one X chromosome, inherited from the mother. For this reason, X-linked traits cannot be passed from father to son.

zygote: the cell that results from the fusion of a male and a female gamete. A fertilized ovum (egg cell) is a zygote.

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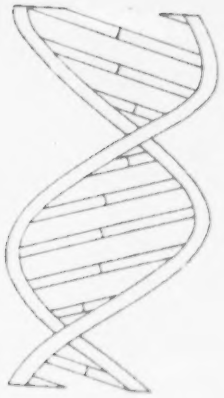
Classroom Activities

This component of the module provides six classroom activities. Material is divided into

- teacher pages, containing suggestions to teach each activity and including annotated student pages;
- special copymasters, containing material needed for handouts or to make overhead transparencies;
- student pages, containing procedural material to copy for the students' use.

Please see Section I, pages 5-7 of the *Overview for Teachers*, for a description of how to use the activities.



Teacher Pages for Classroom Activities

Please note that we provide a summary of the nature and methods of science (NMS) concepts and genetics concepts used in each activity.

Engage Activity
Scientific Investigation

NMS Concepts

- Science depends on data derived from careful observation and experimentation.
- Scientifically useful observations and experiments are those that others can repeat.
- The measurements and descriptions that scientists use must be universal so that one scientist can understand or repeat the work of others.
- These requirements help scientists to communicate effectively, to verify work done by others, and to detect errors in their own work and in the work of others.

Genetics Concepts

This activity does not address genetics concepts.

Focus

This brief and easy activity helps students to think about one of the hallmarks of scientific investigation: careful observation, carefully recorded. The activity provides a mechanism to introduce the general topic of the nature and methods of science. Unlike the other activities of this module, the Engage Activity does *not* require any knowledge of genetics. For this reason, the activity can be used at the start of a biology course, prior to a study of genetics, to introduce how science works. Alternatively, the Engage Activity can introduce the other activities of the module.

Objectives

As students complete this activity, they should

1. understand that careful observation, measurement, and recording of data are essential to science;
2. make their own observations, measurements, and recordings;
3. use their own observations, measurements, and recordings, and those of other students, to compare the utility of different types of data;
4. experience the importance of standardized measurement; and
5. discuss the difference between *observation* and *inference*.

Estimated Time

30 minutes

Preparation and Materials

You will need to provide the following for each team of 3 students:

- metric ruler
- 20-cm piece of string

- unshelled peanuts to fill one small bowl (remove all discolored, cracked, or broken peanuts)
- balance
- magnifying glass

Introduction

Although students often read about the methods of science at the start of a science course, few students internalize and use that knowledge without direct experience. The Engage Activity does not address causal explanations of natural processes, but it does show a number of the fundamental methods of science, including the need for careful observation and precise note-taking if scientific work is to be communicated to other scientists and repeated (see Section III of the *Overview for Teachers*). Standardized measurements and terminology also help with this process. This activity shows some characteristics of careful observation and of the power of accurately recorded evidence.

Strategies for Teaching the Activity

The Engage Activity should be simple and fun, although its message is very powerful. Keep a quick pace. You may want to compare the issues addressed in Questions 5 and 6 of the Analysis with the six questions posed in Section III of the *Overview for Teachers*.

Annotated Student Material

Separate student pages contain the material shown in **bold** typeface.
Here, we provide an annotated version of student materials to help you conduct the activity.

Procedure

Divide the class into teams of 3 and provide each team with a set of the materials. Students within a team share materials, but students work individually. Each student observes the peanut he or she chooses.

1. **Share materials with your team, but work individually. Select a peanut and carefully observe it to determine the distinguishing characteristics that identify this particular peanut. Record your observations on a piece of paper. *Do not mark or crack the peanut.* You may use the equipment provided to help you with your observations.**

Allow no more than 5 minutes for this step.

2. **Return each team member's peanut to the bowl. Mix up the peanuts.**

3. **Use your notes to find your peanut again.**

Allow no more than 2 minutes for this step.

4. **Raise your hand if you are *absolutely certain* you have found your own peanut.**

Have one student calculate the percentage of students who raised their hands and write this number on the chalkboard.

5. **What evidence did you use to locate your peanut and distinguish it from the others in the bowl?**

Sample student responses:
- I measured it.
- I described its shape.
- I drew it.
- I traced it.
- I described how it smelled or looked.
- I found its mass.

6. **Exchange your team's bowl of peanuts and observation notes with those from another team. Now work individually with one set of observations from another student and try to find the particular peanut it describes.**

Allow no more than 5 minutes for students to identify the new peanuts.

7. **Raise your hand if you are *absolutely certain* that you have found the correct peanut.**

Again, have a student calculate the percentage and record this number on the chalkboard.

Analysis

1. What observations were most valuable in finding a specific peanut?

Students should recognize that the most helpful information was that which others could easily understand and apply. This information is objective and has universal, transferable value —for example, length, circumference, width measured in centimeters, or mass measured in grams. Quantitative information is helpful if accurate and standardized. The least helpful information likely was qualitative, that is, information whose interpretation is more subjective—for example, "It's pretty big; it smelled good; it has an interesting shape."

2. What role did your notes or the notes of another student play in helping you to locate a particular peanut? (If your memory was a better guide, what does that say about your notes?)

If students' memories were more helpful than their notes, their observations likely did not produce quantitative data. Notes preserve the accuracy of observations and make them transferable. This issue provides an opportunity to emphasize the importance of careful note taking and of communication in science.

3. People often confuse *observations* with *inferences*. *Observations* are collected using your senses, either directly or expanded by technology using devices such as microscopes, X-ray machines, or microwave sensors on satellites. *Inferences* are ideas or conclusions based on what you observe or already know. Using this distinction, which of the following statements are observations and which are inferences?

- **If this peanut is roasted, the seeds will not germinate.**
  -inference
- **The shell has a rough surface.**
  -observation
- **The shell is uniformly colored.**
  -observation
- **The peanuts came from a plant.**
  -inference
- **The shell has two lobes and is smaller in diameter between them.**
  -observation
- **This peanut will taste good.**
  -inference
- **Squirrels would eat these peanuts.**
  -inference
- **The surface markings on the shell are in rows, running lengthwise.**
  -observation

4. Now, look at your notes and label any inferences that you included.

Emphasize that both observation and inference are important in science, but that these two processes should not be confused. Furthermore, the validity of an inference generally increases with the amount of supporting data. For example, the inference that a given trait is genetic becomes more valid if the trait also occurs in many offspring.

Sometimes, however, even many repeated observations do not confirm an inference beyond question, and we must, therefore, always be cautious about our inferences. For example, we infer that dogs wag their tails because they are happy, and there are many thousands of observations that support this inference. Without direct (and unlikely) confirmation from dogs, however, our inference remains as such.

5. What counts as evidence in science?

At this early stage, you may want to use this question primarily to stimulate thinking about what is required of scientific evidence. Students already may see that careful observation and measurement, universal units of measure, reliance on data, and the ability to repeat an investigation with the same results are a few of the things that characterize a scientific approach to asking questions and seeking answers about the natural world.

6. What makes science objective? Why is objectivity important?

Use the question to poll student opinion, rather than looking for specific answers. Objectivity in science depends on rigorous methods, such as the need for credible evidence. Objectivity helps build the durability of scientific knowledge by connecting it closely to reality rather than to unsubstantiated opinion.

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Activity 1
Standing on the Shoulders of Giants

NMS Concepts

New work builds on old work; the scientific community requires supporting, credible evidence to accept an explanation; credibility depends on the rigor of investigation (precision and replicability); science reflects the culture in which it takes place (minor concept).

Genetics Concepts

The activity reviews fundamental (Mendelian) concepts traditionally taught in genetics and in basic molecular genetics. (See Section V of the *Overview for Teachers*.) These concepts are listed below.

- parental source for inheritance
- chromosome theory of inheritance
- segregation
- independent assortment
- DNA as the genetic material
- sex determination
- genetic code
- linkage
- mutation

Focus

Students combine a brief review of basic genetics with an initial exploration of how scientists use evidence to support explanations of genetic phenomena. The activity directly addresses the first four of the six questions raised in the discussion of methods of science in the *Overview for Teachers* (Section III). Students also indirectly consider the cultural context of the history of scientific discovery.

Students arrange milestone explanations in a conceptual sequence to see that ideas in genetics are interconnected. They then compare their sequences to the actual history of these genetics milestones. Students also evaluate the relative worth of different types of evidence on two levels: credibility and usefulness.

Objectives

As students complete this activity, they should

1. review some of the basic concepts of genetics;
2. recognize and use criteria for determining the credibility of scientific evidence, including precision, replicability, and controlled observation;
3. recognize the association (relevance) between credible evidence and a particular scientific explanation (milestone concept);
4. recognize that new work builds on old work; and
5. build an understanding that genetics has a history based on accumulated knowledge and a strong record of evidence.

Estimated Time

One 50-minute class period

Preparation and Materials

Students will work in 8 teams. To save paper, you may want to laminate the Milestone Cards and Evidence Cards so that you can reuse them. You will need to provide the following:

- 8 sets of Copymaster 1-1, *Milestones in Understanding Genetics*, cut apart (1 set per team)
- 1 overhead transparency of Copymaster 1-2, *Historic Sequence of Milestones*, or 1 copy for each student
- 1 copy of Evidence Cards corresponding to a particular milestone for each team; there will be a *different* set of cards for each team (see Copymaster 1-3)
- chalkboard, flip chart, large sheet of paper, or overhead projector to display the milestone concepts in Part I
- flip chart or butcher paper for an NMS poster (optional)

Copymasters used in this activity

Copymaster 1-1
Milestones in Understanding Genetics

Copymaster 1-2
Historic Sequence of Milestones

Copymaster 1-3
Evidence Cards

Introduction

This activity challenges students to explore the methods of science during a review of fundamental concepts in genetics. A brief discussion of the methods of science is included here for your convenience. For a more detailed discussion, see Section III in the *Overview for Teachers*.

How do we know what we know? This activity deals with two aspects of science that help to answer that question: (1) scientific explanations require credible evidence, and (2) new work builds on old work.

The relationship between evidence and explanation is built on several assumptions. The evidence must be credible according to scientific criteria such as accuracy and repeatability. Authority or fame alone does not establish validity for a particular hypothesis or for opinions offered as evidence. Recognition of the authority or fame of the proponent of a scientific idea may attract attention, but this notoriety in itself is not sufficient for the scientific community to accept the idea unless sufficient credible evidence supports the claim. Evidence also must relate to the issue in question; even credible evidence is not useful when it does not address the question under consideration.

Another step to determine what we know scientifically is to examine an explanation for the soundness of its reasoning. A good explanation starts with accurate assumptions, is guided by credible evidence, and is built through logical connections. If this process is done well, the explanation will have predictive power. Because many scientific explanations aim to discover causal relationships, explanations can be tested according to their ability to predict specific outcomes of the proposed causal event. Causality is a related, but not central, concept in Activity 1, and you may want to expand your discussions to include it. Question 1 of the Analysis is a good place to help students understand what is important about causality and how to establish it. A description of causality is included in Section III of the *Overview for Teachers*.

Finally, science is embedded in cultural history. Science proceeds as a chronological sequence of discoveries, but the paths it follows largely reflect the culture that supports it. Topics of concern to scientists at a particular time reflect many aspects of societal values. For example, if society views cancer, heart disease, and AIDS as important problems, agencies in the public and private sector will make funds available for research in those areas. Research that attracts attention also depends on the current level of technology for acquiring, storing, and analyzing data. Sometimes, a creative idea or question cannot be formulated as a testable hypothesis because of the limitations in technology, resources, or existing information. In these cases, the great idea must wait until history creates the right setting for it.

Strategies for Teaching the Activity

The foregoing aspects of science are incorporated into the tasks of this activity. Although the NMS concepts may not be entirely new to students, these

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concepts often are not presented in a way that makes them useful. A student may have a concrete definition of how science works, but may not be able to *apply* the concept either in thinking or action. This activity, like much of the module, is designed to take the students' understanding of the methods of science that extra step into experience.

In Part I of this activity, students see how new work builds on old work and how milestone explanations attempt to establish a causal relationship. Students arrange the milestones into a sequence that makes connections between ideas, focusing on the concepts rather than on the dates of discovery. (Knowing the dates of the discoveries is *not* the objective.) Ask students to describe the basis for the sequence of milestones they construct—for example, simple to complex or general to specific—and to speculate why this sequence might differ from the historical sequence. Emphasize that the historical sequence is not necessarily "the right answer," but do not hesitate to challenge what appear to be conceptual flaws in a student's sequence. For example, molecular details about mutation and the genetic code would not precede knowledge that DNA is the genetic material.

In Part II, students focus on the role of credible evidence to support a valid scientific explanation. In each team, students study four pieces of evidence to judge their credibility and their usefulness relative to a particular milestone explanation in genetics. Each team has a different milestone. You may want to have the class define "credible" in terms of evidence. In the Annotated Student Material, we suggest questions at the start of Part II to stimulate thinking about this topic before the teams begin their work.

The questions in the Analysis help to make the aspects of the nature of science *explicit* for your students, but do not assume that students will recognize these characteristics without reinforcement. At this time, students may begin to brainstorm ideas for a poster about the nature and methods of science. If you use this technique, students will add ideas to this NMS poster throughout the module. You will need a way to display the collection of student ideas about science, perhaps using a large sheet of butcher paper. The task of adding ideas to this poster should be open-ended, and student responses will vary widely.

Note from the field test: Teachers found that the task of putting milestones into a meaningful sequence drew comments from some students who normally were nonparticipatory.

The following summary of the structure of this activity should help you understand the intent of each part.

Activity 1 at a Glance

Part I: **Milestones in Understanding Genetics**
In a jigsaw fashion, teams build a meaningful sequence of the milestone explanations. Students compare the actual history of the milestone explanations with their own sequence and think about the significance of any differences.

Part II: **How Good Is the Evidence?**
Students review the concept of credible scientific evidence. Each team evaluates four evidence cards for credibility and judges whether the credible evidence supports the team's one milestone explanation in genetics, thus exploring the requirements for an explanation to be accepted as scientifically valid.

Analysis: Students reflect on many aspects of the nature of scie[illegible] They may begin to summarize these ideas on a poster to be used throughout the module.

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Annotated Student Material

Separate student pages contain the material shown in **bold** typeface.
Here, we provide an annotated version of student materials to help you conduct the activity.

If you make a scientific discovery, will people still rely on it one hundred years later? Scientists continue to use the theories of inheritance described by Gregor Mendel (Figure 1-1)—they are remarkably durable after more than a century. Since the rediscovery of Mendel's work in about 1900, biologists have made great strides in determining the mechanisms of heredity. Knowledge about genetics has expanded in the last two decades with technical advances in molecular biology and, most recently, with the work of the Human Genome Project (HGP). This huge project will identify genetic relationships (maps) and chromosomal locations of all human genes and will attempt to determine the DNA sequence for the entire genome of *Homo sapiens*. Mapping and sequencing will be done for other species, too, including selected bacteria, yeast, a plant, and several animal species.

Discovery in the HGP or any field of science occurs in stages. Similarly, the history of genetics is much more than a simple record of dates, names, and discoveries; it is an account of how our understanding of inheritance and the gene has grown and changed. Modern geneticists (Figure 1-2) are "standing on the shoulders of giants" who came before them.

courtesy of Dr. Vítězslav Orel, Mendelianum, Moravian Museum, Brno, Czech Republic

Figure 1-1 Gregor Mendel (1822-1884), a pioneer in the study of inheritance: His explanations were based on observation of traits, use of careful records, and the mathematical analysis of his data.

Procedure

Optional Introduction

You may want to introduce this activity with a brief preliminary discussion about how scientific knowledge is built. An interesting way to start the discussion is to ask, "Can you recall a scientific explanation that was once held to be valid and later found to be inaccurate? Describe that explanation and how it changed."

If students do not respond, suggest an explanation such as the geocentric conception of the cosmos. Point out that it appeared sensible to assume that the sun, moon, stars, and planets revolved around the Earth because they appeared to move across the sky while the Earth felt stationary to the observer. The astronomer Copernicus gathered evidence through careful observation and mathematical calculations to provide a different explanation: the Earth and the other planets orbit the sun (a heliocentric view). Although the center was perceived differently, the idea of orbits remained. Another example of an idea that changed is that of a flat Earth. Students should be able to cite evidence (such as Magellan's

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voyage around the world and photographs from space) that refutes this idea.

Another explanation that changed in light of new evidence is that for the cause of disease. For years, people thought factors such as bad air, getting caught in the rain, or having evil spirits caused disease. These views gradually changed and, in the mid-nineteenth century, scientists provided convincing proof of the germ theory as the basis for communicable disease. The central assumption of germ theory is that microorganisms can invade other organisms and cause illness. The French scientist Louis Pasteur took one large step toward acceptance of that explanation when he dispelled the notion of spontaneous generation. Pasteur, in a series of experiments using thin-necked flasks and sterile techniques, showed that organisms did not grow spontaneously from nonliving matter. He also found direct evidence to support the germ theory of disease when he identified three types of microorganisms that were pathogenic for silkworms, showing the causal connection between a pathogen and a disease. A German scientist, Robert Koch, also supplied evidence for this theory with his discovery of the bacterial pathogen that causes anthrax in cattle.

Earlier notions about causes of disease, such as getting cold and tired, are not without some merit. These conditions are not primary agents of infectious disease, but our improved understanding of immunology shows us that these factors do contribute to disease by impairing immune function. Most changes in scientific knowledge reflect the expansion of inadequate explanations rather than the expulsion of entirely inaccurate ones.

If your students have a fairly good understanding of molecular genetics, they may appreciate the additional example of discovering introns in eukaryotic genes. Because early molecular biology focused mainly on bacteria, most of which lack introns, the discovery of introns came as a surprise and required a modification in our description of genes. (Figure 13 in the *Overview for Teachers* illustrates introns in gene structure.)

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Figure 1-2 Modern studies in genetics: Although modern geneticists use molecular techniques such as cloning and sequencing, geneticists continue to use microscopic techniques, particularly in cytogenetics.

Indicate that, as they work through this module, students will come to understand more about how scientific knowledge changes and develops, and about how scientists go about their work. Students also will learn about some new findings in genetics.

Part I: Milestones in Understanding Genetics

Much of the information about genetics in your biology textbook would have amazed

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Magellan's voyage also resulted in a reconceptualization of time. Although Magellan was killed in the Philippines before the end of the voyage, his crew kept careful records of dates during the 3-year journey. When they returned to their home port in Spain, they found that they had lost a day. This led to understanding that the Earth's rotation results in different time zones—and even a different day—on some parts of the globe. We now acknowledge and correct for this phenomenon with the International Date Line.

The article by P.A. Small and N.S. Small, Mankind's Magnificent Milestone: Smallpox Eradication, *The American Biology Teacher*, 58(5):264-271, provides a nice overview of the application of scientific process to the eradication of an infectious disease.

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biologists a hundred years ago. Those scientists, driven by curiosity to answer complex questions of heredity, slowly pieced together layer after layer of the milestone explanations that we now accept as valid. The most significant explanations stand as milestone events, each of which marks a great shift in our understanding. Think about what scientists needed to know *before* they could add each new milestone to the body of genetics knowledge. You are going to build a sequence of milestone explanations. When you do, your sequence may reflect the actual progress of genetics during the last hundred or so years, or it may reflect other ways that history could have played itself out during these early years of discovery.

Assign students to teams and distribute a set of milestone explanations to each team.

1. **Your team will receive a set of eight milestone explanations of inheritance. Decide how these milestone explanations could form a meaningful sequence, and be prepared to report your sequence and the reasons you chose it.**

After the teams have had a chance to build a sequence, poll the class for examples of the choices each team has made. You may want to have each team turn in a written sequence, or you may want to call on two or three teams to report. Ask the students to explain the criteria they used to sequence the milestones. A handy way to display results of different teams is to prepare a poster for each milestone and have a student place the posters in sequence, or prepare a set of milestones strips on overhead transparency film for display. To start the discussion, you could display a milestone from the middle of the actual sequence, choose another milestone, and ask whether it should come before or after the first one.

Important: Keep in mind (and emphasize for the students) that their job is *not* to guess the dates and chronology of these events. Instead, their task is to reason *how* the milestone explanations might build in a logical way. Keep the discussion brief, and do not press for consensus.

2. **Your teacher will show you the actual sequence of milestone events that occurred in the history of genetics. Compare it to the sequence you helped build with the class. Might the events have occurred just as easily in the order you built?**

Display an overhead made from Copymaster 1-2 that shows the historical sequence of milestone concepts and/or distribute a copy to each student. Emphasize to the class that the *connections* between discoveries are far more important than the dates on which the discoveries occurred.

The historical sequence for these events is given in Copymaster 1-2, and the sequence presented is somewhat arbitrary in that some ideas gained strength from multiple experiments that occurred over a number of years. For instance, an early experiment that indicated that DNA is the genetic material took place in 1944, but additional evidence provided in 1952 convinced the scientific community. The work of Mendel, which might have influenced research in genetics in the latter part of the nineteenth century, failed to do so because it was not recognized widely and understood until around 1900. The actual sequence of events in scientific history does not necessarily represent the only, or even the best, sequence in terms of logical connections because scientists are at times limited by technology or make imperfect choices about the next question to be answered.

3. **What technologies or cultural issues might have influenced the timing of the milestones and other discoveries in genetics?**

Sample student responses include:

- the use of a microscope,
- staining techniques,
- computers, and
- the laboratory techniques of molecular biology.

Less obvious answers include:

- better communication among scientists,
- money available to support research,
- political interests at the time,
- rediscovery and openness to Mendel's paper,
- the development of more sophisticated statistics, and
- the use of computers to store and compare data.

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Part II: How Good Is the Explanation?

The milestone explanations you have been using have lasted for many years. Why? Use this part of the activity to explore how we know whether a scientific explanation is on the right track and, thus, whether it will survive the test of time.

If your students have a basic grasp of what is meant by *credible evidence*, continue to Steps 4 and 5. If not, conduct a brief discussion to establish this idea. You may want to use Question 3 from the Analysis here as an introduction. Otherwise, this question will serve as a review of this part of the activity.

The student version of the Evidence Cards and their corresponding Milestone Explanation is provided in Copymaster 1-3. An annotated version appears in these teacher pages.

4. **Your teacher will give your team a set of Evidence Cards and one Milestone Card. Your first task is to evaluate the Evidence Cards and keep only those that are credible. To determine whether the information on any given Evidence Card is credible, discuss with your teammates the criteria you can use to evaluate the evidence. Write your reasons for accepting or rejecting the stated evidence.**

Allow a few minutes for teams to make their choices. This step is brief because the "bogus" evidence cards are fairly obvious. The value of this step is that students must articulate their criteria. Ask a few teams to give examples of why they accepted or rejected evidence.

5. **Now decide whether the evidence you retained is helpful in supporting or refuting the milestone explanation. Explain your decision. *(Hint: Some evidence will be helpful; other evidence may not be related to the milestone explanation.)***

Allow enough time for students to compare ideas about the relationship between evidence and the genetics concept on the Milestone Card, but keep their discussion brief. Ask several teams to justify the helpfulness of the evidence relative to the milestone explanations. (To keep the activity moving, you may not want to have all the teams do this.)

You may need to remind students that, for evidence to support a scientific explanation, the evidence must be related to the main ideas in that explanation. Related evidence should help to distinguish between one explanation and competing views. If the explanation discusses causality, supporting evidence needs to show a constant and regular association between the stated cause and effect. For example, in 1927, after H.J. Muller exposed fruit flies to heavy doses of X rays, offspring of the exposed flies exhibited mutations. This experiment can be repeated with the same results, supporting the notion that radiation is a causal agent of mutations. Later experiments provided a more detailed explanation of the cause by demonstrating the molecular damage in DNA that results from exposure to X rays.

Analysis

Not all scientific discoveries are great milestones that change our understanding of the natural world. Scientists put an enormous amount of work into even relatively simple discoveries, as you would expect when you consider the rigors of investigation. These small pieces provide a valuable part of a larger puzzle. Gradually, we build our understanding of inheritance. The rarity of great leaps in understanding can be a frustrating aspect of scientific work.

Science is carried out by people who must earn a living and who want to fulfill personal goals, factors that might influence their work. Think about the social and cultural setting in which research takes place as you respond to these questions.

1. What does science try to do?

Sample student responses include:

- It makes discoveries.
- It finds facts.
- It explains things.

For additional discussion, see Section III of the *Overview for Teachers*, page 14. You may want to introduce the idea of *causal explanations*.

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2. How do we know an explanation is on the right track?

Sample student responses include:

- The explanation predicts events accurately.
- An explanation is supported by good evidence.
- More than one line of evidence supports the explanation.
- The explanation is consistent with other scientific knowledge.

For a full discussion, see Section III of the *Overview for Teachers*, page 15.

3. What counts as credible evidence in science?

Sample student responses include:

- The evidence was the result of laboratory work (an experiment).
- There is statistical evidence (numbers) or the experiment yields the same result when repeated.
- Experiments include adequate controls.
- The evidence survives challenges by the scientific community.
- The evidence is accurate.

You might want to record some of the responses on the chalkboard or on a large sheet of paper under the heading "Criteria for Credible Evidence." Keep the list visible in the classroom as a prompt for Steps 4 and 5.

4. Mendel developed a simple, yet elegant, system to explain inheritance. What has happened to his system?

Mendel's work has endured because it still explains a great many of our observations about inheritance. Scientists, however, have proposed many new explanations about inheritance since Mendel's time. Those that satisfied the requirements of scientific investigation have become incorporated into an ever-expanding body of knowledge about inheritance.

5. Begin to make a poster that records your ideas about the characteristics of science, if your teacher instructs you to do so.

Have students brainstorm ideas and record them on poster paper under the heading "Nature and Methods of Science." Display this NMS poster in the classroom. Encourage students to add ideas throughout the module.

Sample student responses about the characteristics of science include:

- More than one source of evidence makes an explanation stronger.
- Evidence needs to be repeatable.
- Explanations show the connection between a cause and the resulting event.
- Mendel's explanations are valid today.
- A new discovery must fit with an existing explanation or the explanation would have to change.
- New work builds on old work.
- When people are concerned about inherited disease, there will be more money for genetics research.
- A famous name is not enough to get your explanation accepted.
- You have to do experiments.
- You have to share your data.

Annotations to the Copymasters: Copymasters 1-1 and 1-3

Here, we number each milestone in sequence, followed by its corresponding evidence. Actual copymasters omit numbers to avoid influencing students.

Milestones in Understanding Genetics - No. 1

Question:
Why do offspring resemble their parents?
Milestone Explanation:
Parents contribute genetic material to their offspring.

Evidence 1A:
A scientist looked through a microscope at dividing cells in the tail fins of a salamander. As mitosis proceeded, she saw that chromosomes moved apart in equal numbers into the newly forming daughter cells. Other scientists observed this phenomenon in cells undergoing mitosis.

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This evidence is

- credible; the statement is based on careful observation and is repeatable.
- helpful, but only partly supportive because, although it shows a possible role for chromosomes in passing information to daughter cells, mitosis and cell division in tail fins have nothing to do with inheritance from parents to offspring.

(This is one of the observations that led to an explanation of DNA replication and cell division [W. Flemming, 1879].)

Evidence 1B:
A scientist crossed pea plants and carefully recorded the appearance of certain traits in the offspring. When he crossed a strain that has only purple flowers with one that has only white flowers, the offspring always had purple flowers. When he crossed these offspring to produce the next generation, however, he saw both colors of flower in the new offspring in regular proportions.

This work was repeated later by other scientists who saw the same results.

This evidence is

- credible; this experiment is repeatable with the same results.
- helpful; this information provides evidence that flower color is a trait inherited from parents, and that both parents may contribute to the phenotype of future offspring. The white color trait is not lost, but hidden; there must be at least two factors involved, one from each parent.

(This is one of Mendel's classic experiments, reported in 1865 and repeated by others in 1900. The implication is that each parent contributes one of the alleles for flower color, but that purple color is the dominant trait.)

Evidence 1C:
Jorge noticed that a classmate, Susan, has curly hair. When he met her mother, he noticed that she also has curly hair.

This evidence is scientifically bogus; although it suggests that genetic information passes from parents to the offspring (Susan), the evidence is so limited in its scope that it is not of much value. The curly hair may result from other than genetic influences; for example, maybe Susan and her mother have used perms to curl their hair.

Evidence 1D:
Mendel said that characteristics of offspring likely come from something the offspring get from their parents.

This evidence is scientifically bogus; stated this way, the information is unclear and unsubstantiated. If it said "Tom" instead of "Mendel," people would be even less likely to credit the statement. Authority without a basis in scientific evidence is not meaningful in supporting a scientific explanation.

MILESTONES IN UNDERSTANDING GENETICS - NO. 2

Question:
How are traits distributed in offspring?
Milestone Explanation:
Alleles of one gene segregate in the formation of gametes.

(Reproductive cells [gametes] form during meiosis. Each gamete contains one allele from the pair of alleles present in the parent.)

Evidence 2A:
People say that sons express the traits of the father, while daughters have all the mother's characteristics.

This evidence is scientifically bogus; it is based on hearsay and lacks a scientific basis.

Evidence 2B:
Offspring in each generation are identical.

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This evidence is scientifically bogus; the statement is not correct, and there is no information about how the observation was made. Even if it were credible, the evidence would not be helpful because the evidence does not address the distribution of traits.

Evidence 2C:
Mendel speculated that traits are inherited based on discrete units of inheritance. He tested the law of segregation by observing height in several generations of pea plants. He saw a distribution of tall to dwarf in the F2 generation of 3:1. Then the F2 plants were fertilized with their own pollen (selfed). Mendel found that the dwarf F2 plants produced dwarf F3 plants, but two-thirds of the tall F2 plants produced mixed offspring, dwarf and tall. This F3 test of segregation has been repeated many times with the same results.

This evidence is

- credible; the evidence is drawn from careful observation and collections of quantitative data; it is repeatable.
- helpful; the ratios in F2 and F3 generations fit the predictions based on the segregation of alleles in the production of gametes.

Evidence 2D:
A scientist named W.S. Sutton observed chromosomes in cells undergoing meiosis. He noticed that the chromosomes behaved in a way that is consistent with Mendel's observations about inheritance patterns. Many other observations of meiosis by other scientists confirmed this behavior of chromosomes in the nucleus.

This evidence is

- credible; other scientists have replicated Sutton's findings.
- helpful; this is evidence that chromosomes behave in a way that is consistent with Mendel's laws of inheritance and will fit with their mathematical predictions.

(This observation by Walter S. Sutton in 1903 helped establish the chromosome theory of inheritance. This same evidence was used to support another milestone explanation; this overlap is a common occurrence in science.)

MILESTONES IN UNDERSTANDING GENETICS - NO. 3

Question:
Where are genes located?
Milestone Explanation:
Genes are located on chromosomes.

(This idea is the chromosome theory of inheritance. In eukaryotic cells, genetic material is located in the nucleus in structures called chromosomes, for their dark-staining characteristic. The name comes from the Greek words *chroma* [color] and *soma* [body].)

Evidence 3A:
Using staining techniques and a microscope, C. Nageli discovered a set of structures in the nuclei of cells. Other scientists observed that these structures change and become visible with a microscope at certain times in the cell cycle. Years after Nageli's observation, a developmental biologist, W. Roux, observed these structures in the cell nucleus, and another scientist, W. Waldeyer, saw the structures and named them chromosomes.

This evidence is

- credible; other scientists have replicated Nageli's findings.
- somewhat helpful in that it establishes that chromosomes exist. It is not conclusive, however, because there is no evidence about their genetic role.

(C. Nageli discovered chromosomes in 1842; Wilhelm Roux saw them in 1883, but did not have evidence of

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their role in inheritance. W. Waldeyer gave chromosomes their name in 1888.)

Evidence 3B:
A scientist named W.S. Sutton observed chromosomes in cells undergoing meiosis. He noticed that the chromosomes behaved in a way that is consistent with Mendel's observations about inheritance patterns. Many other observations of meiosis by other scientists confirmed this behavior of chromosomes in the nucleus.

This evidence is
- credible; other scientists have replicated Sutton's findings.
- helpful; this is evidence that chromosomes behave in a way that is consistent with Mendel's laws of inheritance and will fit with their mathematical predictions.

(This observation by Walter S. Sutton in 1903 helped establish the chromosome theory of inheritance.)

Evidence 3C:
A scientist, T. Boveri, showed that sea urchin embryos develop normally only when they have a full set of chromosomes. Embryos with more or fewer chromosomes than the normally observed number did not develop properly. Many other scientists have made the same observations in other organisms.

This evidence is
- credible; it is precise, testable, and repeatable.
- helpful; it connects cause and effect to genotype and phenotype.

(This observation by T. Boveri in 1903 was one line of evidence that led to the chromosome theory of inheritance.)

Evidence 3D:
A professor at Harvard thinks that chromosomes contain genes.

This evidence is scientifically bogus because it is imprecise. The professor has provided no details, and the evidence is based on the fame of the university alone. There is no substantiating scientific evidence. Perhaps the professor is a specialist in something unrelated to biology and knows little about genetics.

MILESTONES IN UNDERSTANDING GENETICS - NO. 4

Question:
What determines the sex of an organism?

Milestone Explanation:
In most sexually reproducing organisms, special chromosomes determine sex.

(Humans have sex chromosomes, designated X and Y. The combination of sex chromosomes in an organism determines its sex.)

Evidence 4A:
Many studies have shown that human females have two X chromosomes, and human males have one X chromosome and one Y chromosome. Patricia Jacobs and other scientists also showed that, although the normal human sex chromosome complement is XX or XY, other patterns do occur rarely. For instance, in humans, XXY individuals are male, and XO individuals are female.

This evidence is
- credible; it is precise, and several lines of investigation support it.
- helpful, especially when added to our knowledge that chromosomes are the mediators of inheritance. This is evidence that sex determination results from the lack of the Y chromosome in females, or the presence of the Y chromosome in human males.

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Evidence 4B:
During their lifetime, human males produce many sperm, but females produce only a few eggs. Many years of studies showed that females are born with all the egg cells they will ever have (although the eggs must mature individually during successive menstrual cycles). Males, however, produce millions of new sperm cells every few days until a very advanced age.

This evidence is

- credible; the conclusions are based on "many years of studies."
- not helpful; the information is correct, but it has nothing to do with sex determination.

Evidence 4C:
A scientist named C.E. McClung found that grasshoppers produce equal quantities of two different types of sperm, one of which contains an extra chromosome. Three years later, two other scientists, N. Stevens and E.B. Wilson, determined that female grasshoppers have two copies of one particular chromosome, whereas males have only one.

This evidence is

- credible; it is precise, and other scientists can replicate the data.
- helpful; this is evidence that the extra chromosome in grasshopper females determines sex.

(These are the studies of C.E. McClung in 1902, and N. Stevens and E.B. Wilson in 1905.)

Evidence 4D:
There is a saying that a pregnant woman can determine the sex of her child by eating spicy foods to produce a male or cool foods to produce a female.

This evidence is scientifically bogus; this evidence is based on hearsay and folklore. In addition, the question and milestone explanation address the genetic determination of sex in offspring; by the time a woman knows she is pregnant, the genotype of the potential offspring already is determined. What she eats or drinks can affect the developing phenotype of her fetus, sometimes adversely (alcohol, for example, can cause a variety of problems in the developing fetus, including low birth weight and retardation), but it cannot affect the sex of the fetus.

MILESTONES IN UNDERSTANDING GENETICS - NO. 5

Question:
Why do some traits occur together in offspring?
Milestone Explanation:
Some genes are located on the same chromosome (linkage).

Evidence 5A:
The host of a popular talk-show about sports says that the best baseball pitchers have brown eyes.

This evidence is scientifically bogus; this comment is based on hearsay rather than scientific evidence, so it is not credible. At first glance, the comment may appear relevant to students because it suggests that two traits, pitching well and eye color, are related. Even if there were data to support the statement, many other factors might be involved, for example, light sensitivity in blue-eyed players. This situation does not indicate a genetic connection between two heritable traits.

Evidence 5B:
Many microscopic studies show that chromosome pairs can exchange material during meiosis, resulting in a new combination of alleles in that pair of chromosomes. This phenomenon is genetic recombination, which results from crossing over.

This evidence is

- credible; it is based on "many microscopic studies."
- somewhat helpful, but not strongly supportive. This observation suggests that some genes on

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one chromosome may not behave as though they are linked when they are separated by a substantial distance, such that recombination can occur.

Evidence 5C:
Three scientists demonstrated that purple flowers and long pollen were inherited together in the sweet pea more often (more than 75% of the time) than predicted by Mendel's law of independent assortment (50%).

This evidence is

- credible; the scientists conducted experiments and kept track of their data.
- helpful; this is evidence that these genes are associated in some way.

(The experiment is the 1906 observation of W. Bateson, E.R. Saunders, and R.C. Punnett; it demonstrates linkage—a noted exception to Mendel's law of independent assortment. The two genes are on the same chromosome and are not always separated by crossing over during meiosis.)

Evidence 5D:
A study of human pedigrees shows that certain traits such as hemophilia and color blindness occur at a much higher frequency in males than in females. These traits appear to depend on the inheritance of mutations located on the X chromosome. When a man has both of these traits, studies show that there is a greater than 50% chance that any brothers will have both disorders, or neither one.

This evidence is

- credible; it relies on the observation of multiple cases and on careful mathematical analysis.
- helpful; in this case, the two traits are on the same chromosome (X) and are not inherited independently, supporting the idea that they are linked. The distance between genes on one chromosome determines how tightly they are linked. If the genes are very tightly linked, the probability is low that they will be separated during crossing over.

(This work was done by Julia Bell and J.B.S. Haldane in the 1930s and was the first to show linkage in humans. It provided early groundwork for the impetus of the Human Genome Project to map all human genes and identify those that are disease-related.)

MILESTONES IN UNDERSTANDING GENETICS - NO. 6

Question:
What molecular component in chromosomes carries genetic information?
Milestone Explanation:
DNA carries genetic information.

Evidence 6A:
Three scientists purified DNA from bacteria that grew in smooth colonies. They put this DNA into bacteria that normally grew in rough colonies. The bacteria that had been given the DNA produced many generations of offspring that formed smooth colonies. This experiment produced the same results when repeated.

Other scientists (many years later) transferred a specific fragment of DNA from bacteria to a plant, and a bacterial trait appeared in the plant.

This evidence is

- credible; it is based on experimentation, and others have replicated the results.
- helpful; this is evidence that DNA contains information that determines phenotype, such as traits that affect the appearance of a bacterial colony or particular genes in a plant. The *accumulation* of evidence that supports an explanation many years after it was first proposed is common and shows the durability of scientific knowledge. You may want to point out this phenomenon after the students have assembled their conceptual sequence of milestone explanations.

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(The first observation is the classic experiment by O.T. Avery, C.M. MacLeod, and M. McCarty, performed in 1944. They transformed pneumococcus by transferring DNA from one strain to another. Modern genetic engineering provides many examples of transformation by DNA, even across species boundaries. For instance, the gene for a toxin from *Bacillus thurengensis* that is effective against insects has been inserted into several species of plants including tobacco, tomato, and cotton.)

Evidence 6B:
Two scientists studied viruses to determine how they infect bacteria. They labeled the DNA and the protein components of the viruses using radioactive chemicals. This allowed them to trace the movement of the DNA and protein. Only labeled DNA entered the bacterial cells during the infection process. Other investigations repeated these studies.

This evidence is

- credible; the evidence results from experiments that others have replicated.
- helpful; this is evidence that DNA, not protein, is responsible for infection by bacteriophage viruses.

(This is the 1952 experiment of A.D. Hershey and M. Chase.)

Evidence 6C:
Scientists have extracted DNA from many different cell types in one organism and from the cells of many different species.

This evidence is

- credible; it is based on work with numerous samples.
- helpful, but certainly not conclusive. The fact that all cells appear to have DNA supports the hypothesis that DNA is the genetic material. All cells, however, also have proteins, carbohydrates, and lipids, so this evidence is in no way conclusive.

Evidence 6D:
Scientist Francis Crick and a student named James Watson agreed that DNA might be the genetic material.

This evidence is scientifically bogus. Without scientific evidence, the opinion of these men proves nothing. Students might be naive about this bogus evidence because these scientists did go on to discover the structure of DNA (although even that evidence alone does not prove its role as genetic material).

MILESTONES IN UNDERSTANDING GENETICS - NO. 7

Question:
How is the genetic information used to make proteins encoded?
Milestone Explanation:
In DNA, a triplet of nucleotide bases encodes each amino acid in the resultant protein.

Evidence 7A:
To determine how the genetic code might work, scientists noted that DNA has four different bases that can be arranged in various sequences. The code must be able to specify the 20 different amino acids found in proteins. Mathematical principles predict the following about the genetic code:

one-base code	specifies 4 amino acids at most
two-base code	specifies 16 amino acids at most
three-base code	specifies 64 amino acids at most
four-base code	specifies 256 amino acids at most

This evidence is

- credible; it is based on mathematical principles that are clearly demonstrable and testable.
- helpful; the three-base code has the minimal complexity required to encode twenty amino acids. This evidence does not prove the triplet nature of the genetic code, but it is supportive and it suggests a testable hypothesis.

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Evidence 7B:
Investigators found that removal of three nucleotides from a gene causes the resulting protein to lose one amino acid. However, removal of one or two nucleotides from a gene causes much more disruption in the resulting protein structure. Other scientists quickly repeated these experiments and got the same results.

This evidence is

- credible; it is based on experiments that others have replicated.
- helpful; this is evidence that the protein-coding information occurs in groups of three nucleotides.

(This is the 1961 experiment where Francis Crick, L. Barnett, S. Brenner, and S.J. Watts-Tobin, used a mutagenic chemical [proflavin] that adds or removes nucleotides from DNA. A one- or two-nucleotide change results in a frameshift of the protein-coding information; removal of three nucleotides simply removes one amino acid from the protein and usually is less disruptive to protein function. You may want to take time to discuss this idea of a frameshift mutation and the significance of a triplet code.)

Evidence 7C:
Many types of chemical analysis have shown that DNA contains about equal amounts of four different components (the nucleotides, which contain bases abbreviated A, G, C, and T). In contrast, proteins are made of 20 different components (amino acids), and they vary in amount in different proteins.

This evidence is

- credible; it is based on "many types of chemical analysis."
- not directly supportive of the milestone explanation. In fact, this early observation led many scientists to conclude that protein is the genetic material because its structure appeared to be capable of more variation. DNA appeared to be too regular. The difficulty arose because scientists did not know the actual structure of DNA that permits the *sequence* of four bases to produce an enormous number of variations (hence, different genes). The variation evident in protein (phenotype) is actually the *result* of genetic information rather than its *source*.

Evidence 7D:
A shampoo is advertised as containing DNA and able to enrich hair.

This evidence is scientifically bogus (but typical); the claims included in advertisements are not always substantiated, although they are supposed to be. Sometimes, advertising combines two unrelated phenomena in the hope that the consumer will infer a connection. For example, this advertisement combines "contains DNA" (which could be true) and "enriches hair" (which implies but does not state that DNA does this; it is a questionable claim in any event). In addition, there is no scientific evidence to support this association. Furthermore, even if DNA did enrich hair, that fact does not address DNA's role as genetic material (hair is protein, not a living cell).

MILESTONES IN UNDERSTANDING GENETICS - NO. 8

Question:
How does a new, heritable trait appear in a population?

Milestone Explanation:
Mutations change the structure of DNA in reproductive cells (gametes).

Evidence 8A:
People who build large muscles through exercise will have children who also have large muscles.

This evidence is scientifically bogus; it is not substantiated by any data from careful observation and measurement. In addition, even if it were credible, this evidence would not be helpful as an explanation of *heritable* change. Strong parents may pass along a genetic makeup for heavy build to their children, but

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this transfer does not depend on the acquired trait of muscle building from exercise by the parent.

Evidence 8B:
A scientist named Hermann J. Muller exposed fruit flies to increasing doses of radiation in the form of X rays. He kept careful records of the number of mutant traits that appeared in their offspring. Muller found that there was a direct correlation between the number of mutations and the amount of radiation: more X rays produced more mutant offspring. (Later research showed that X rays damage chromosomes.) Other scientists have repeated this experiment, and similar experiments have been repeated many times.

This evidence is

- credible; it is based on careful observation and a precise record of results. Others have replicated Muller's results.
- somewhat helpful; it suggests a causal relationship, although it does not directly address DNA structure as the basis for physical change.

(Muller received the 1946 Noble Prize for this [and related] work, which he reported in 1927.)

Evidence 8C:
Investigators found that removal of three nucleotides from a gene causes the resulting protein to lose one amino acid. However, removal of one or two nucleotides from a gene causes much more disruption in the resulting protein structure. Other scientists quickly repeated these experiments and got the same results.

This evidence is

- credible; it is based on evidence that others have replicated.
- helpful; this is evidence that the protein-coding information occurs in groups of three nucleotides.

(This is the 1961 experiment where Francis Crick, L. Barnett, S. Brenner, and S.J. Watts-Tobin, used a mutagenic chemical [proflavin] that adds or removes nucleotides from DNA. A one- or two-nucleotide change results in a frameshift of the protein-coding information; removal of three nucleotides simply removes one amino acid from the protein and usually is less disruptive to protein function. This same evidence was used to support another milestone explanation; this overlap is a common occurrence in science.)

Evidence 8D:
Investigators at the Toronto Hospital for Sick Children studied the DNA of children who have cystic fibrosis (CF). The investigators also studied the parents of these children. They found that these children and their parents have changes in their DNA that are not present in unaffected children or in persons who do not carry the CF gene. Further investigation has revealed more than 600 different DNA mutations in the CF gene.

This evidence is

- credible. The investigators collected data on CF patients and their parents and compared those data to other data from unaffected persons and noncarriers. Other investigators found additional mutations in the CF gene.
- helpful; the evidence shows a relationship between changes in genotype and changes in phenotype. In addition, the work builds on our basic understanding of Mendelian genetics, in this case, autosomal recessive inheritance.

(This is the 1989 work of Lap Chee Tsui and his colleagues in Toronto. This group isolated the CF gene.)

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Activity 2
Puzzling Pedigrees

NMS Concepts

Existing explanations are tested with new evidence; new evidence is used to build hypotheses.

Genetics Concepts

This activity reviews traditional (Mendelian) inheritance patterns, and introduces the concept of extranuclear (mitochondrial) inheritance.

Focus

Activity 2 permits students to review pedigrees and major patterns of traditional (Mendelian) inheritance. Students also discover a pattern of inheritance that does not "fit" those with which they are familiar. The students use pedigrees that show this new pattern and related data to discover that there are modes of genetic transmission, such as mitochondrial inheritance, that do not follow Mendelian patterns. The activity lets students experience the cycle of evidence and explanation through which scientific knowledge is built, tested, used, and modified. When reliable data do not fit with existing explanations, the data are *not* discarded; instead, existing explanations change or new explanations are built.

Objectives

As students complete this activity, they should

1. review familiar patterns of inheritance: autosomal dominant and recessive, X-linked dominant and recessive;
2. discover that some patterns of inheritance do not follow Mendelian patterns;
3. use some of the methods of science: observe, gather evidence, propose explanations for patterns of transmission in the puzzling pedigrees, and look for additional evidence to support or refute their new explanation; and
4. add to the NMS poster (optional; see Activity 1).

Estimated Time

One 50-minute class period

Preparation and Materials

You will need to provide the following:

- overhead projector
- overhead transparency of Copymaster 2-1, *Pedigrees A-H* (optional)
- overhead transparency of Copymaster 2-2, *Pedigrees I and J* (optional)

- overhead transparency of Copymaster 2-3, *Pedigrees I and J* (optional)
- coins for simple statistical model (at least 1 coin per team)
- Copymaster 2-4, *Building an Explanation* (1 copy per student)
- Copymaster 2-5, *Science Articles* (1 copy per student)

Copymasters used in this activity

Copymaster 2-1
Pedigrees A-H (optional)

Copymaster 2-2
Pedigrees I and J (optional)

Copymaster 2-3
Pedigrees I and J (optional)

Copymaster 2-4
Building an Explanation (worksheet)

Copymaster 2-5
Science Articles

Introduction

This activity forms a bridge between what students already know about fundamental patterns of inheritance and modes of transmission that likely are new to them. The activity challenges students to understand that scientific knowledge in genetics is both lasting and flexible, with emphasis on the development of new explanations when explanations based on our current understanding are not adequate to account for new observations. Students review traditional patterns of inheritance, discover a new and puzzling pattern (mitochondrial inheritance) that they attempt to explain, and articulate the way they have used scientific processes in this activity. (See Section V in the *Overview for Teachers* for information about extranuclear inheritance.)

An interesting consequence of our awareness of mitochondrial inheritance is the ability to trace maternal lineages for the human species back to ancient times. The topic is popularly called "the mitochondrial Eve story," and it has received much media attention. You might direct students to the following articles about this interesting and somewhat controversial topic:

- Thorne, A.G and M.H. Wolpoff. The multiregional evolution of humans, *Scientific American* 266(4):76-83, April 1992;
- Wilson, A.C. and R.L. Cann. The recent African genesis of humans, *Scientific American*, 266(4):68-73, April 1992; and
- Chapter 3 of *The Neandertal Enigma*, by James Shreeve, 1995, William Morrow and Company.

Primary literature sources for your own use include:

- Cann, R.L., M. Stoneking, and A.C. Wilson. Mitochondrial DNA and human evolution, *Nature* 325:31-36, 1987;
- Vigilant, L., et al. African populations and the evolution of human mitochondrial DNA, *Science* 253:1503-1507, 1991.

Strategies for Teaching the Activity

A chart summarizing the structure of this activity is included at the end of the Strategies discussion. It should help you understand the intent of each part of the activity.

Prior to using this module, students must have completed a basic study of genetics. Please see Figure 12 in the *Overview for Teachers* for a list of fundamental genetics concepts; we assume that students are familiar with these ideas. Part I of Activity 2 reviews basic Mendelian inheritance to provide a contrast with mitochondrial inheritance. If your students are not familiar with the information presented in Figure 2-2, or if they are not experienced in using pedigrees, you should teach that basic material before using this activity. For simplicity of comparison, we have maintained the same family structure in the pedigrees. Ask students to *justify* their choices as they assign known patterns of inheritance to Pedigrees A-H.

In Activity 2, the constructivist approach to teaching is obvious in the way students search for a new concept of inheritance (mitochondrial inheritance) to explain some puzzling data. (See Section I of the *Overview for Teachers* for a brief discussion of constructivist teaching.) Students' *thinking* is as important as their finding the correct answer. They exercise their powers of observation and reasoning as they propose and test various hypotheses to explain a surprising pattern of inheritance. In so doing they experience the methods

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of science. Help make this aspect of the activity overt so that students recognize the ways in which they are "doing science."

In Parts II and III, allow students to explore possible explanations, but insist on carefully stated hypotheses, testing, and sound reasoning. Discourage guessing. You can help students distinguish hypothesis formation from guessing by probing for students' justifications of their responses. "It's autosomal dominant" could be a scientific hypothesis or a wild guess. If students offer this explanation, ask them to describe the evidence. (This approach also is useful in the review in Part I.)

A scientific hypothesis is based on existing observations, and then it is tested through additional observation and experimentation. Emphasize that sometimes we make an observation that is not adequately explained by existing concepts; we then must seek a new explanation. In Part III, remind students that it is okay not to have a final answer, but they must document their observations and their reasoning carefully on the worksheet in Copymaster 2-4. Students need not reach the explanation of mitochondrial inheritance prior to the Analysis. If all students reach the correct conclusion prior to completing all the steps, skip ahead to the Analysis, but do insist that students justify their conclusions. The articles titled *"Extra" DNA* and *Fertilization: Sperm Meets Ovum* (Copymaster 2-5) describe extranuclear DNA as a concept larger than the example of mitochondrial inheritance alone. This conceptual approach will help students contrast what they learn about extranuclear inheritance with the more traditional view of nuclear inheritance.

This activity affords many opportunities to make students conscious of the methods of science they are putting to use. For example, the suggestions offered in Figure T2-2 (page 96 of the Annotated Student Material) show one way to call students' attention to the methods of science at work in their own hands and mind.

Please note that in the pedigrees and throughout the activity we have consciously avoided the usual terminology of "an affected individual" to refer to people who show the trait in question. Our reason is that "affected" generally refers to a disorder, and all too often students come away from their study of inheritance thinking that genetics is only about genes that do not work properly. We want to help students realize that *most* genes we inherit are functional, as shown by the fact that we are functional organisms. To accomplish this awareness, we indicate that a "trait is present" instead of saying an "individual is affected."

The final emphasis of the Analysis is to show how science works. Students reflect on what they have done in this activity and add to the NMS wall poster begun in Activity 1 (optional; see Activity 1, page 80 for an explanation).

Activity 2 at a Glance

Part I: **Review of Inheritance Patterns**
As a review, students examine Pedigrees A-H and identify them according to traditional patterns of inheritance with which they are familiar.

Part II: **Puzzling Pedigrees**
Students examine Pedigrees I and J, which do not fit traditional patterns, and recognize the need for a new explanation.

Part III: **Testing an Explanation**
Students develop hypotheses to explain the puzzling pedigrees. They use a coin toss to test their initial hypothesis, and they use new information (science articles) to refine their explanation.

Analysis: Students discuss how they have used the methods of science in this activity, thinking about how scientific explanations arise.

Hints to shorten the activity: Assign the review of Pedigrees A-H as homework, and follow this assignment with a brief class discussion. Alternatively, have students analyze only four pedigrees for the review, including one example of each traditional pattern of inheritance.

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Annotated Student Material

Separate student pages contain the material shown in **bold** typeface.
Here, we provide an annotated version of student materials to help you conduct the activity.

How do scientists decide the direction for their research? For example, scientists want to know how genes are involved in cancer. This problem is too large and complex to tackle all at once.

Scientists, therefore, break large problems into smaller, focused parts. They propose a testable explanation, called a hypothesis, to try to answer one of the smaller questions. These hypotheses show where and how to look for answers.

As scientists make observations and record data, they usually find that the new evidence reinforces what they already know. Sometimes, however, the new data do not fit what is known. If the *evidence is reliable*, scientists cannot just ignore it. Instead, they must look for new explanations to extend or modify what is known. In this activity, you will put your skills of observation and your previous knowledge of heredity to work to study some puzzling patterns of inheritance.

Procedure

Part I: Review of Inheritance Patterns

1. **Determine the *most likely* pattern of inheritance for each of the pedigrees shown in Figure 2-1. To help you, Figure 2-2 lists the characteristics of the four patterns of inheritance that you studied in the genetics unit of your biology class. Your teacher will direct you to work on this task alone or with a partner. You will have 10 minutes to complete this task.**

Figure 2-1 Pedigrees showing the inheritance of eight human traits

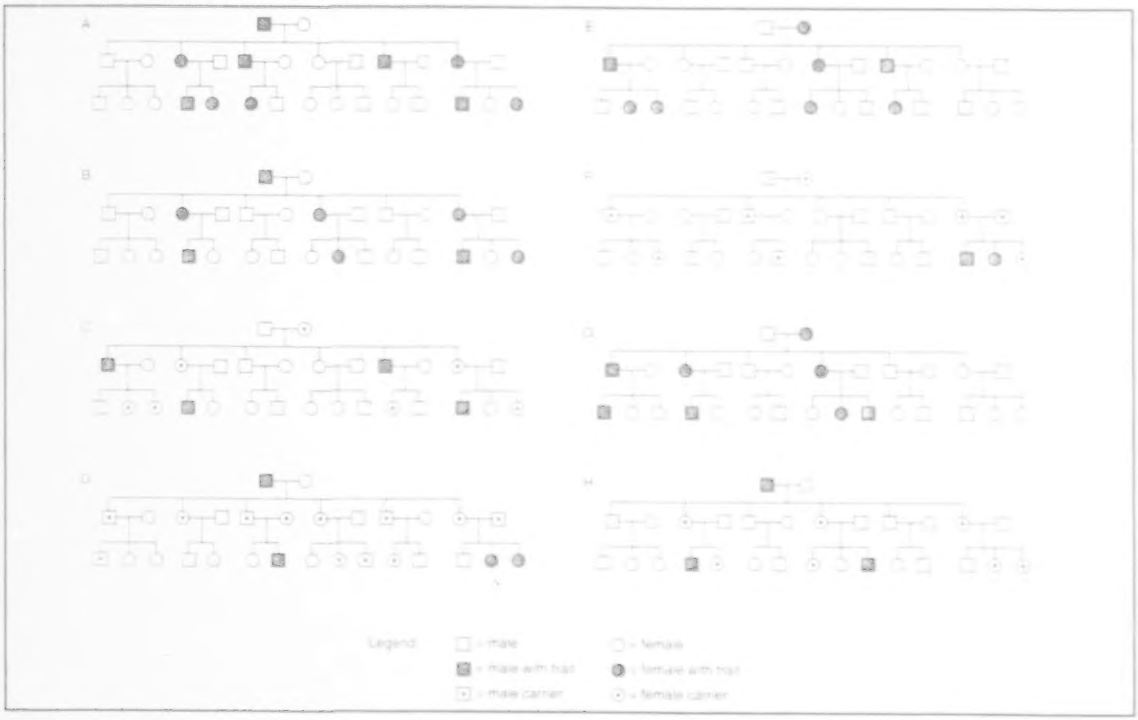

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Figure 2-2 Four patterns of inheritance

Autosomal dominant	Autosomal recessive
Males and females are equally likely to have the trait. Traits do not skip generations (generally). The trait is present whenever the corresponding gene is present (generally). There is male-to-male transmission.	Males and females are equally likely to have the trait. Traits often skip generations. Often, both parents of offspring who have the trait are heterozygotes (they carry at least one copy of the allele). Only homozygous individuals have the trait. Traits may appear in siblings without appearing in their parents. If a parent has the trait, those offspring who do not have it are heterozygous carriers of the trait.
X-linked dominant	**X-linked recessive**
All daughters of a male who has the trait will also have the trait. There is no male-to-male transmission. A female who has the trait may or may not pass the gene for that trait to her son or daughter.	The trait is far more common in males than in females. All daughters of a male who has the trait are heterozygous carriers. The son of a female carrier has a 50 percent chance of having the trait. There is no male-to-male transmission. Mothers of males who have the trait are either heterozygous carriers or homozygous and express the trait. Daughters of female carriers have a 50 percent chance of being carriers.

Note from the field test: Students found the summary of traditional inheritance patterns presented in Figure 2-2 to be very useful. You may want to incorporate this chart into your earlier study of Mendelian inheritance and have students refer to it when they do Activity 2.

Decide whether individual or team work will be more productive and, if appropriate, form teams. Limit the work to 10 minutes and then conduct a brief class discussion so each student can determine the accuracy of their work. Projecting an overhead transparency of pedigrees A-H (Copymaster 2-1) may aid discussion. Insist that students provide evidence and reasoning to support their choices and do not just list the answer. Remind students that they should propose *the most likely* pattern of inheritance. Some pedigrees may demonstrate more than one pattern.

The most likely patterns of inheritance for the Pedigrees A-H are given in Figure T2-1. (Pedigrees I and J will be presented to students in Part II).

Part II: Puzzling Pedigrees

2. Study two new pedigrees (Pedigrees I and J) shown in Figure 2-3. *Both pedigrees illustrate the same trait.* Try to identify the inheritance pattern illustrated by these two pedigrees. Explain your responses, stating specific examples to support your explanation.

Pedigrees I and J demonstrate mitochondrial inheritance (Figure T2-1). To help with the discussion, you might want to project an overhead transparency of Pedigrees I and J (Copymaster 2-2). Make certain that students understand that both pedigrees show the *same trait*. Solicit a variety of responses.

Figure T2-1 Patterns of inheritance for the pedigrees

A & G	autosomal dominant
D & F	autosomal recessive
B & E	X-linked dominant
C & H	X-linked recessive
I & J	mitochondrial (presented later)

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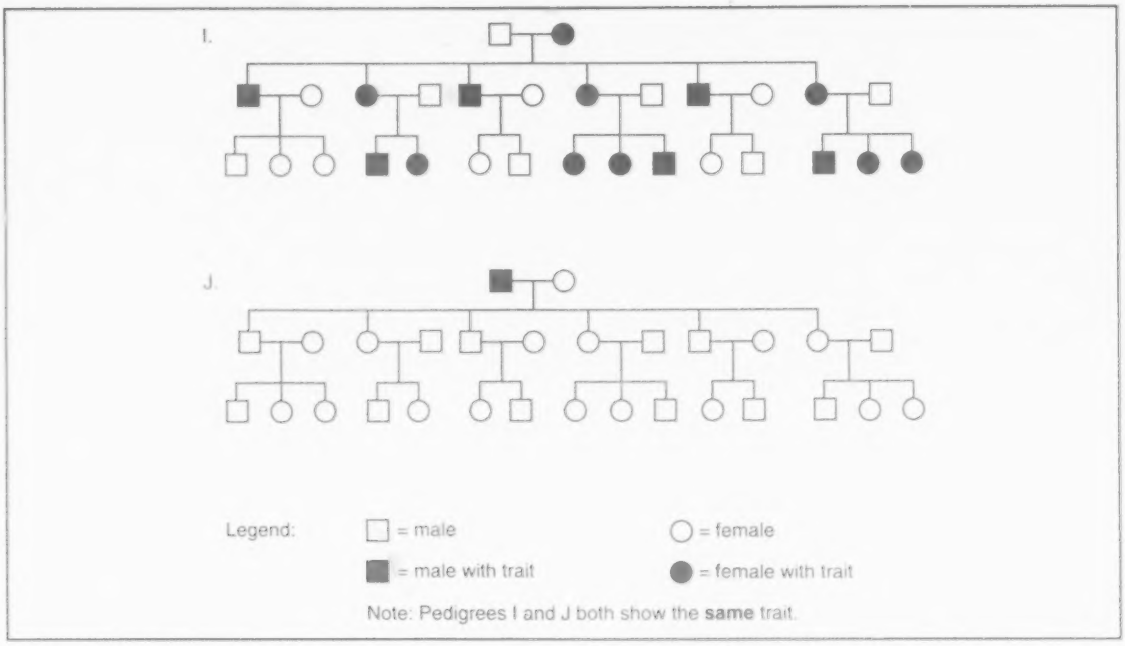

Figure 2-3 Two puzzling pedigrees

Pedigree J should be a real puzzle to the students because there is no obvious connection to the patterns in Figure 2-2. Students might identify Pedigree I as autosomal dominant. If not, ask a few questions so that students propose this pattern. For example: "Does the trait skip generations?" (Students may say it does in pedigree J; actually, it vanishes.) "Do the parents of individuals with the trait have the trait themselves?" (Female parents have the trait.) Alternatively *you* could propose autosomal dominant inheritance as a challenge to students.

NOTE: These data do not rule out a dominant, maternal-effect allele, but students are unlikely to suggest this explanation.

Part III: Testing an Explanation

How good is the explanation of inheritance you suggested in Part II? When you suggested an inheritance pattern, you were making a hypothesis. A scientific hypothesis is a *testable* explanation. To determine how good your hypothesis is, use evidence to test it.

3. Analyze the data (evidence) you have observed from the pedigrees to see whether they support or conflict with your hypothesis. (Your teacher will provide a worksheet for your convenience.) Record your explanation for the inheritance patterns in Pedigrees I and J as "Hypothesis 1." (Remember that both pedigrees demonstrate the *same* trait.) Next, list evidence that *supports* your explanation and evidence that *conflicts* with it. Refer specifically to Pedigree I or J as you report this evidence.

Distribute a copy of the worksheet (Copymaster 2-4) to each student to help them organize their explanations. If students choose autosomal dominant, conflicting evidence includes the fact that all six children of the second generation in Pedigree I have the trait. This situation could suggest that the mother is homozygous for the trait. In that case, however, Pedigree J does not fit the same pattern.

4. You can reason, calculate, or do experiments to test a hypothesis. For example, assume that the mother in the first generation of Pedigree I is heterozygous. For a hypothesis of "autosomal dominant":

a. Consider each child singly. What is the

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probability that the mother will transmit the gene in question? (You can calculate the probability based on what you know about autosomal dominant inheritance.)

The probability is 1/2 (50%) for each conception.

b. You actually can model the events in the pedigree and use the data to test this hypothesis. Use a coin to represent the two alleles involved in this trait. Heads will represent the allele responsible for the trait. Tails will represent the allele that does not produce the trait. Model the inheritance shown in the second generation by tossing the coin six times, once for each child. Record the results, using a chart like the one illustrated in Figure 2-4.

Occasionally, a student will get six heads in the coin toss. If so, the following analysis of the third generation should clarify this point. Lead a class discussion that ties the model of the coin toss to the proposed genotypes based on the hypothesis and to the actual phenotypes shown in the second generation of Pedigree I. The data likely will show that there is only a small chance—$(1/2)^6$ or 1/64—that all six children in the second generation of Pedigree I will inherit the allele responsible for the trait, as would be true for autosomal dominant inheritance.

If you want to emphasize the importance of *sample* size for accurate data, or in case a student gets six heads, you may choose to analyze the next generation for additional data. Do this with Pedigrees I and J or use Pedigrees I′ and J′ (Copymaster 2-3), which show an extra generation.

This analysis can best be done family by family so that students can see the pattern in terms of the sex of each parent for that generation. Again, data from the coin toss should refute the likelihood that the observed phenotypes result from autosomal dominant inheritance. This conclusion forces the students to return to the original problem because our present knowledge of inheritance patterns does not provide an explanation for inheritance shown in these pedigrees.

Record results from each toss in the appropriate column.	
heads (allele for trait is present)	tails (allele for trait is absent)

Reminder: In autosomal dominant inheritance, if the allele is present, the trait will be present.

Figure 2-4 A coin-toss modeling experiment

c. Your coin toss gave you empirical (observable) data. You also can calculate the likelihood that all six children inherited the trait from the female parent. (*Hint: Recall your answer to Question 4a, and remember that the probability for each child is based on a separate event. Use the product rule, based on the second law of probability, to find the probability for all six children.*)

If students are familiar with the second law of probability, they should be able to calculate the probability as $(1/2)^6$ or 1/64. If they are not familiar with this law, explain it to them and let them do the calculations. (The second law of probability states that the probability that independent events will occur together is the product of their individual probabilities.)

After discussing the results of the coin tosses and what they may mean, you may find it helpful to review what the students have done to this point. Emphasize that they have used several important methods of science in their work, as shown in Figure T2-2, on page 96.

5. Suppose that the mother exhibiting the trait in the first generation of Pedigree I is homozygous for a dominant trait. Would that explanation be consistent with the results you observed in her offspring (the second generation)? Use the data from the coin test to support your conclusion. What about the results in the third generation of Pedigree I?

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Figure T2-2 Methods of science used in Activity 2

- Students may have noticed that Pedigrees I and J do not fit any of the four classic patterns of inheritance and thus they *identified a problem or question*.
- The examination of the pedigrees is an example of *observation*.
- The proposal that Pedigree I could illustrate autosomal dominant inheritance is a testable *hypothesis*. (Students may have other hypotheses as well.)
- Coin tossing is designed to *test this hypothesis by collecting data*.
- Coin tossing is an example of a *model system*.

The observation that all six offspring in the second generation show the trait is consistent with autosomal dominant inheritance if the first-generation mother is homozygous. However, the results in the third generation are inconsistent with this explanation because offspring of males who have the trait do not inherit and express it. To be certain, however, more examples (a larger sample size) would be helpful. Once again, you may want to use Pedigree I.

6. Examine Pedigrees I and J again carefully and summarize your observations on your worksheet.

Students may use the additional data in Pedigrees I and J if you have introduced this material.

a. Indicate whether your tests confirm or refute the pattern you hypothesized. Record your response as your "conclusions." (*Hint: Your conclusion could be in the form of a question.*)

b. If your earlier choice was refuted, can you now propose a new explanation? If so, record it under "Hypothesis 2" on your worksheet. If not, do not worry. Steps 7-9 may help you.

In Pedigree J, only the father in the first generation has the trait. None of his children or grandchildren has it. In Pedigree I, the mother in the first generation has the trait and all of her children have it. In the third generation of Pedigree I, all children of the second-generation females have the trait. None of the children of the second-generation males has the trait.

7. Use Questions 7a and 7b to help you find a new explanation:

a. Examine each instance where the trait is passed to offspring. What do you observe about the source of the inherited trait?

The source is the mother.

b. Mendelian genetics assumes that in all cases each parent contributes equally to the genotype of the offspring. Do the data shown in Pedigrees I and J demonstrate this idea?

No. Based on these pedigrees it appears that the trait shows up more often if it is inherited from the mother; of course, these data are limited.

Modify your conclusions or propose a new hypothesis if your ideas have changed.

At this point, do not expect students to have a complete explanation of the mechanism they are observing. A good response might be:

Observation: The trait in each pedigree shows up with surprising frequency in later generations. It is too frequent in I and too rare in J to be explained easily.

Conclusion: There may be some unknown inheritance pattern or process at work here that makes this allele transfer from the mother only. (Or, stated as a question, "What mechanisms of inheritance would result in a pattern of inheritance exclusively from the mother?")

As a final attempt to build a new explanation, use Questions 8 and 9 to guide your thinking. When you have recorded your best explanation, continue to the Analysis. (Your explanation may be incomplete. What is important is that you justify your reasoning with evidence.)

8. Could the inheritance of an allele carried on the X or Y chromosome explain the pattern of inheritance in Pedigrees I and J? Explain your response.

Females have the trait, so the allele is not carried on the Y chromosome. Pedigree J shows no transmission of the gene in question; if the allele were on

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the X chromosome, you would predict presence of the trait in offspring unless the inheritance were recessive. In the latter case, the pattern shown in Pedigree I is not likely: too many offspring have the trait.

9. Consider the four patterns of inheritance in Figure 2-2. What do they assume about the location of genetic material in the cell?

These patterns result from the behavior of genetic material in the nucleus.

a. In humans, sperm cells and egg cells transmit genetic information to offspring. How do these cells differ?

Discussion should focus eventually on one of the major differences between the egg and sperm: size. An egg cell is about 1,000 times larger than a sperm cell. An egg consists of a nucleus and a considerable amount of cytoplasm. The sperm essentially is a nucleus with a tail. The illustration included in the news article, *Fertilization: Sperm Meets Ovum* (Copymaster 2-5), will help establish this point when you distribute copies later in the activity.

b. In addition to a complete set of chromosomes (46), what does the developing zygote need to grow and develop? *(Hint: What structures are in the cytoplasm?)*

A constant source of energy is necessary for growth and differentiation. Do not be too concerned if students do not mention all the organelles and structures, but they should mention mitochondria.

Analysis

Distribute Copymaster 2-5, which includes two science articles to be used in the Analysis. Have students read the introductory paragraph of the Analysis. If you are approaching the end of a class period, assign the questions as homework. Ask the students to respond to the questions in the Analysis. Follow this assignment with a brief discussion to address any problems students have understanding the mechanism involved in mitochondrial inheritance.

1. Read the two articles your teacher distributes. What bearing does the information in the articles have on your explanation of Pedigrees I and J?

If students have not already identified mitochondrial inheritance as the explanation for Pedigrees I and J, they should do so now. The first article, *"Extra" DNA*, informs students that organelles such as mitochondria and chloroplasts contain their own DNA. The second article, *Fertilization: Sperm Meets Ovum*, reminds students that only the maternal mitochondria survive in the zygote. Combined, these ideas should lead students to the explanation of mitochondrial inheritance for Pedigrees I and J.

If they have made this explanation earlier, these articles provide additional support.

2. What lasting scientific knowledge about inheritance did you use in this activity?

Sample student responses include:

- Parents contribute genetic material to their offspring.
- Alleles of one gene segregate in the formation of gametes.
- A special pair of chromosomes determines sex in humans.
- DNA carries genetic information. This is a lasting explanation that is part of the understanding of mitochondrial inheritance.
- Mutations change the structure of DNA.
- Some traits show dominant inheritance while some show recessive inheritance.

3. What new explanations for inheritance did you use in this activity?

Sample student responses include:

- Mitochondria have their own DNA (mtDNA).
- Some human traits result from the action of genes in mtDNA.
- There is genetic material (DNA) in addition to that in the nucleus (extranuclear inheritance).
- Some traits are inherited from the maternal source exclusively.
- Mitochondria are inherited maternally.

Help students view mitochondrial inheritance as an example of the broader concept that genetic material is not limited to the nucleus.

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4. What methods of science did you use in this activity?

Sample student responses include:

- I used observation, as in the work with the pedigrees and the coin toss.
- I acquired evidence (pedigree, coin toss, article on mitochondrial DNA).
- I tested new evidence against existing explanations.
- I formulated a hypothesis.
- I modeled an experiment about likelihood (coin toss).

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Activity 3
Clues and Discoveries in Science

NMS Concepts

Explanations that do not account for new evidence are inadequate; careful observation and data collection provide credible evidence; new work builds on old work; cultural influences can affect scientific research.

Genetics Concepts

Students use traditional Mendelian patterns of inheritance and learn that gene alteration can occur during inheritance. They learn that unstable trinucleotide repeats help to explain genetic anticipation.

Focus

In this activity, students encounter genetic anticipation in the human genetic disorders Huntington disease (HD) and myotonic dystrophy (DM) and discover that traditional genetics concepts do not readily explain this phenomenon. Students then use evidence at several levels to demonstrate anticipation and to provide an explanation of the genetic mechanisms that underlie the process. The activity is designed as a mystery, where students use clues to solve the mystery of genetic anticipation. Students reflect on (1) the connection between *evidence* and *explanation* in describing causal processes; (2) the lasting yet new nature of our genetics knowledge; and (3) the historical context of scientific understanding.

Objectives

As students complete this activity, they should

1. develop a brief historical perspective of our understanding of Huntington disease and myotonic dystrophy and their impact on families;
2. acknowledge the lasting ability of Mendelian and other traditional genetics concepts to explain most of the genetic processes involved in these disorders;
3. use case-history evidence, pedigree construction, and new molecular data to demonstrate genetic anticipation and to construct an explanation for its underlying mechanism (instability of trinucleotide repeat sequences in genes associated with Huntington disease and myotonic dystrophy);
4. recognize and experience the cooperative nature of scientific research by reviewing the historical, step-wise construction of genetics explanations and by cooperating with other students to solve the mystery; and
5. think about how our evolving understanding of the gene influences our perceptions of health and disease.

Estimated Time

75-100 minutes

Preparation and Materials

Students will work in 8 teams. You will need to provide the following:

- 1 copy of Copymaster 3-1, *HD Clues Presenting Familial Relationships and Health Data*, cut apart to distribute to each team as indicated
- 8 copies of Copymaster 3-2, *HD Clues Presenting Molecular Data* (1 copy per team)
- 1 overhead transparency of Copymaster 3-3, *Template for the HD Pedigree* (optional)
- 8 copies of Copymaster 3-3 (1 copy per team)
- 1 copy per student of Copymaster 3-4, *Science Article about a Genetics Discovery*
- 8 copies of Copymaster 3-5, *DM Clues Presenting* (A) *Familial Relationships and Health; and* (B) *Molecular Data* (1 copy of parts A and B per team)
- 8 copies of Copymaster 3-6, *Template for the DM Pedigree* (1 copy per team)
- 8 copies of Copymaster 3-7, *Completed Pedigrees* (optional; 1 copy per team)
- 8 copies of Copymaster 3-8, *History of Huntington Disease - Vignettes* (optional; 1 copy per team)

Students will work in eight teams of approximately four each. Students will assemble the Huntington disease pedigree in a jigsaw fashion as a class activity, using clues contributed from the eight teams. You will need one complete set of familial and health clue slips for HD (Copymaster 3-1) *distributed as indicated among the teams*, and one copy of the molecular clues for HD (Copymaster 3-2) for *each* team. The molecular clues can be cut into separate strips for each student in a team or used as a single sheet that the team consults. You may want to laminate the clues so that they can be reused easily.

For the myotonic dystrophy pedigree, we suggest that you have *each* team use a complete set of familial health clues and molecular data (Copymaster 3-5) and quickly put together the pedigree as a team. You can cut clues apart so that each student in the team works with several clues, or you can use the clues as a single sheet that the team consults. If you like, provide a template for each pedigree (Copymasters 3-3 and 3-6) to help students organize the data. You also may find it useful to make a transparency of the templates so that you can coordinate the class discussion. We have provided the completed HD and DM pedigrees in Copymaster 3-7 for your convenience and in the event you wish to shorten this activity by starting with completed pedigrees.

Copymasters Used in This Activity

Copymaster 3-1
HD Clues Presenting Familial Relationships and Health Data

Copymaster 3-2
HD Clues Presenting Molecular Data

Copymaster 3-3
Template for the HD Pedigree (optional)

Copymaster 3-4
Science Article about a Genetics Discovery

Copymaster 3-5
DM Clues Presenting (A) Familial Relationships and Health; and (B) Molecular Data

Copymaster 3-6
Template for the DM Pedigree (optional)

Copymaster 3-7
Completed Pedigrees (optional)

Copymaster 3-8
History of Huntington Disease - Vignettes (optional)

Introduction

Genetic anticipation is a term introduced in 1911 by F.W. Mott to describe earlier onset of symptoms or greater severity of symptoms in subsequent generations with certain genetic disorders. This phenomenon provides a powerful example of the sequential nature of scientific explanation and the relationship between existing explanations and new evidence. New evidence often challenges existing explanations. For example, scientists observed an unusual feature of several human genetic disorders, including Huntington disease and myotonic dystrophy, that is, the age of onset or severity of symptoms often shifted in subsequent generations of families with these disorders. Many

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years passed, however, before sufficient evidence accumulated to establish the phenomenon clearly. One problem was that traditional Mendelian genetics did not explain genetic anticipation. A better explanation had to await the development of new technologies that would contribute additional lines of evidence, a situation common in scientific investigations.

In the case of genetic anticipation, an initial debate centered on whether the evidence from the case histories represented a legitimate biological phenomenon or resulted from bias in data collection. Given the limitations on collecting data from and about humans, one must be especially careful to avoid bias in the analysis of case histories. Early ideas about anticipation appear in work by the nineteenth century "psychiatrist" Benedict Auguste Morel (the term psychiatrist was not then in use). He spoke of the theory of degeneration, in which progressive severity and earlier onset of an illness from parent to offspring was seen. (See McInnis, 1996, for an excellent review of early ideas about anticipation.) Even when there was enough evidence to confirm the existence of genetic anticipation, existing genetics concepts did not explain how this anticipation could occur. With the development of sophisticated molecular techniques, however, scientists identified the fundamental molecular mechanisms associated with this phenomenon. The genes in several disorders that display anticipation have been shown to contain unstable stretches of a particular trinucleotide repeated many times. (See page 43 in Section V of the *Overview for Teachers* for a more detailed discussion.)

Transmission of the genes associated with HD or DM may result in a change in the number of repeats. There is a threshold level at which instability becomes marked; when the trinucleotide expansion reaches a critical level, severe phenotypic effects result. For example, individuals with more than 39 copies of the trinucleotide repeat CAG found in the mutant HD gene are scored as positive on genetic tests; most likely, they will develop the disorder, unless they die from some other cause first. When the mutant HD gene has many more than 50 repeats, the age of onset is likely to be earlier than in cases with a smaller number of repeats. In addition, there is evidence that the parent of origin makes some difference in the behavior of the mutant HD gene. The age of onset is somewhat earlier if the gene is inherited paternally (Ranen, et al. Anticipation and instability of IT-15 (CAG)N repeats in parent-offspring pairs with Huntington Disease. *The American Journal of Human Genetics* 57(3):593-602, 1995). Apparently, the expansion in repeats is more likely to be greater with transmission from the father than from the mother.

Genetic anticipation in DM results in a change in the age of onset, and in a dramatic difference in symptoms from one generation to another. The unstable repeats in the mutant DM gene contain the trinucleotide CTG. As the number of CTG repeats reaches 50-80, mild symptoms, including cataracts, appear fairly late in life. The repeat number can reach the thousands, and severe symptoms can appear from birth, including muscle disfunction and mental retardation.

Modification of the traditional view of dominant inheritance to include anticipation may seem quite remarkable, but scientists have continued to add to and modify their understanding of genetics since the early twentieth century. When Mendel's laws were rediscovered in 1900, the factors of inheritance were viewed as particulate and fixed so that outcomes from any given genotype would be very similar, if not identical. Over the years, we have learned that a variety of nongenetic factors can affect the phenotype. Environment, for example, often influences gene expression. Organisms reach their full potential height, based on genotype, only if placed in an environment where nutritional and other environmental factors are optimal. Another influence on gene expression results from genes that play a role in the expression of other genes. For example, some inherited anemias may be less severe in individuals with counterbalancing genes whose expression increases the production of red blood cells. Finally, there is a strong element of chance in the expression of many genes in the form of environmental factors or other elements we do not yet understand thoroughly. The genotype establishes the limits of a given phenotype, but the ultimate phenotype reflects a variety of influences.

Some differences in the expression of traits appear as phenomena known as penetrance and variable

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expressivity. Penetrance refers to the proportion of individuals with a given genotype who express the associated phenotype. Penetrance is an all-or-none phenomenon; one either expresses the trait or does not. If every individual with a particular genotype in a given population expresses the trait in question, the trait is said to be completely penetrant. If less than 100 percent of the people with that genotype express the trait, the trait is incompletely penetrant. Variable expressivity refers to the range of physical effects and to the timing of expression for the characteristics of a genetic disorder. Environmental variables, other genes, and chance may influence expressivity and penetrance; these factors can cloud our ability to make exact predictions about the likelihood of particular outcomes of genotypes. Observations related to penetrance and variable expressivity required modifications of early Mendelian models. Although geneticists now take penetrance and variable expressivity for granted, they were as remarkable at the time of their discovery as are recent discoveries such as unstable trinucleotide repeats or genomic imprinting. Section V of the *Overview for Teachers* provides an extensive discussion of the changing concepts of inheritance.

For a more detailed explanation of HD and DM, their clinical aspects, and the discovery of the molecular mechanisms, also see the *Overview for Teachers*, Section V, pages 43-49. In addition, the first genome module from BSCS, *Mapping and Sequencing the Human Genome: Science, Ethics, and Public Policy*, has an extensive description of HD.

One final consideration is an examination of the methods for establishing causation in a scientific explanation. Consider a simple analogy. You go to your car one morning and notice the tire is flat—that is an observation. You examine the tire and find a large nail embedded in it. The evidence suggests a cause for the flat, because you can show the presence of the nail and because sound reasoning (and perhaps the experience from previous flats) shows a mechanism by which a nail could cause the flat—it creates a hole through which air escapes. Unfortunately, while the principle is the same, showing a causal relationship in science often is not so easy. In this activity, students consider the relationship between a large number of trinucleotide repeats and the manifestation of a genetic disorder. The association—like the nail in the tire—begins to establish cause, but the reasoning to show how the presence of repeats causes disease is not yet established. A more extensive discussion of causality is included in Section III of the *Overview for Teachers*, page 14.

Strategies for Teaching the Activity

In this activity, the *reasoning process* is primary. Students use evidence to justify and to modify scientific explanations. Students must propose answers and ideas, but they also must *justify how* they arrived at their conclusions. Students should see that, although the explanation for a new genetic mechanism must be added to the existing body of genetics knowledge to account for genetic anticipation, our fundamental understanding of dominant inheritance is lasting and explains most other features of Huntington disease and myotonic dystrophy. In this activity, students build their explanation of genetic anticipation in stages. First, they use pedigree evidence to support the existence of anticipation. Next, they use molecular evidence to suggest the underlying mechanism.

This procedure offers opportunities for you to make explicit to students several key aspects of scientific investigations. Emphasize that observational data, such as the information from case histories or pedigrees, are important scientific evidence. Many students mistakenly think of experiments as the only source of useful data, but in studies of human genetics, scientists are limited in the types of experiments they can do using human subjects. People marry and have children with whomever they choose, so useful *observation* of the resultant patterns of inheritance is particularly important.

The activity begins as an inquiry patterned after a mystery and is structured to demonstrate the need to use information in a precise manner. The mystery approach and use of clue slips serve mainly to make the activity fun and to arouse interest, although this structure does provide some aspects that model how science is done. For example, the jigsaw approach used for building the HD pedigree reflects the need for communication among scientists and

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gives students some practice with quantitative data as they work out dates of birth, death, and other characteristics of the people in the pedigrees. However, if you prefer not to devote class time to this initial game-like process, skip Steps 2-4 in Part II, and move ahead by distributing the completed HD and DM pedigrees (Copymaster 3-7).

The mystery approach may seem a bit unstructured and even noisy at first, and it is important to keep students focused on the task. We recommend that you keep an open, somewhat unstructured style so that the opening steps (Part II, Steps 2-3) have the feel of a game. In particular, in Step 2, give individual teams only 1-2 minutes to see how their clues could fit together and, perhaps, to suggest a pedigree as a useful way to organize data. You may want to wait until students make the suggestion to build a pedigree (possibly prompted by a question from you about how to organize clues) before you hand out the templates. Keep assembly of the pedigree an active and exciting aspect of this part of the procedure. You can help keep a quick and fun pace by asking questions about specific relationships in the pedigree. For example, ask "Who are these twins?" or "Who is Andrew's father?" Suggestions for subtle guidance of the inquiry appear at several steps in the Procedure. You also can use this part of the procedure as an opportunity to challenge students to read, reason, and calculate carefully as they determine the details of the pedigree.

Students build an explanation of anticipation in the following sequence:

- The opening dialogue establishes the mystery of whether anticipation is real or a function of bias in observation.
- The health data in the HD pedigree support the existence of genetic anticipation in this disorder.
- The molecular data in the pedigree for HD and the science article about trinucleotide repeat expansion suggest a mechanism for anticipation.
- The data for the DM pedigree supply an additional line of evidence.
- The vignettes provide a historical context for discovery about genetic anticipation (optional).

"Activity 3 at a Glance" follows and it summarizes the structure and goals of each part of the activity. *Notice that the information available at each major step is separated by 20 years of research in genetics.*

We have separated the examination of clues into two phases to correspond to two discoveries: identifying the existence of genetic anticipation, and identifying evidence for the underlying molecular mechanism. In this way, the activity has the essence of an open inquiry while offering some guidance to help students make these discoveries. For the activity to be effective, it is *essential* that students distinguish these two levels of discovery.

Activity 3 at a Glance

Part I: **Identifying the Mystery**

Step 1: Students read a dialogue set in 1957.

Outcome: Students recognize the mystery of genetic anticipation.

Part II: **Gathering Clues to the Mystery**

Steps 2-4: Students in each team receive clues about *familial relationships* and *general health* in the HD family. Students build a pedigree to analyze the clues.

Outcome: Students recognize evidence for genetic anticipation. (They lack evidence for the underlying mechanism.)

Steps 5-7: Students in each team receive additional clues that provide *molecular data* about members of the HD family.

Outcome: Students identify evidence for a genetic mechanism that causes genetic anticipation (unstable trinucleotide repeats). This evidence also strengthens the case for genetic anticipation.

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ACTIVITY 3 AT A GLANCE

Step 8: Students repeat the process for a DM family.
Outcome: Additional evidence strengthens the students' explanations.

Part III: **Discovering the History of Genetic Anticipation (optional)**
Students study vignettes that help them see the conceptual history of our understanding of genetic anticipation.

Analysis: Students summarize what they have learned and make connections to NMS.

Annotated Student Material

Separate student pages contain the material shown in **bold** typeface.
Here, we provide an annotated version of student materials to help you conduct the activity.

How do you know that a new scientific idea is correct? Lots of people have good ideas about how to explain what they observe in living systems, but a good idea alone is not enough. Scientists constantly have to decide whether a new idea is valid, and they do so by using the requirements of science. To meet these criteria, a good idea must be based on logical reasoning, and it must be tested, preferably many times and in many different ways. A scientist draws an idea (hypothesis) from early observations of a problem and then collects evidence to determine whether the idea is scientifically valid. If the hypothesis seems to be valid, the scientist will share it with other scientists. They, in turn, may repeat the tests to see whether the evidence is reproducible, or they may add new lines of evidence from different tests. If enough evidence accumulates, the scientific community accepts the hypothesis as valid, and it becomes part of the established body of scientific knowledge. In simple terms, people then refer to the new idea as part of "what they know about genetics."

This approach to building an explanation for a natural process sounds fairly simple, but it can be complicated. For example, how do you tell the difference between discovery of a new process and misinterpretation of data? Such a debate arose in genetics among people who studied two inherited disorders, Huntington disease (HD) and myotonic dystrophy (DM). In this activity, you will step into the shoes of the scientists involved in this debate and use the requirements of science to follow the history of this intriguing investigation. Read the descriptions of HD and DM in Figures 3-1 and 3-2 if you are not familiar with these disorders.

Note: Your students likely have studied Huntington disease. If so, have them summarize what they know about this genetic disorder before using Figure 3-1.

PROCEDURE

Part I: Identifying the Mystery

The following fictitious dialogue and series of questions introduce students to the idea of genetic anticipation. Call the students' attention to the date for the opening dialogue, which is 1957.

1. The dialogue below takes you back in history to the year 1957. Read the dialogue and then answer Questions 1a-1e.

Note that in this dialogue we use the term "chorea"; this name for HD was the common term used in the 1950s.

1957

The year is 1957. **This dialogue is part of a discussion that might have taken place between a physician and a geneticist: we will call them Dr. A. and Dr. B. As you read their discussion, think about *why* they have different views.**

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Dr. A: "I've been seeing a patient named Allen who may have Huntington's chorea. If so, I think he is a good example of genetic anticipation."

Dr. B: "You mean that this disease runs in his family, but is showing up at an earlier age in Allen than it did in his parents or grandparents?"

Dr. A: "Exactly. Allen is only 40, and already he has short periods of memory loss and sudden problems with awkward movement of his legs. When I interviewed him, I learned that his mother died when she was 65, but, starting at age 55, people who knew her said she was a bit 'odd' in her thinking. She spent her last five years in a wheelchair, suffering from severe muscle and movement problems. She appeared to have Huntington's chorea."

Dr. B: "But that doesn't prove that genetic anticipation is a real phenomenon. What do you know about Allen's maternal grandparents and great-grandparents?"

Dr. A: "Not much. His mother's mother died when she was very young, during childbirth, so all we know is that she did not show signs of Huntington's chorea up to the age of 24. Allen's grandfather lived to be about 70, but Allen knew nothing about his general health. But you *know* geneticists have reported cases of anticipation for years. What about Dr. Bell's discussion of it in her 1947 publication in *The Treasury of Human Inheritance*? She makes a good argument for genetic anticipation in another genetic disease, myotonic dystrophy."

Dr. B: "You mean her mention that patients in an earlier generation of a known pedigree generally had only mild symptoms, such as cataracts, when they were middle-aged, while —"

Dr. A: "— while their children and grandchildren had muscle wasting and mental illness, more severe in each subsequent generation—an example of genetic anticipation."

Figure 3-1 Huntington Disease (HD): Summary of Symptoms

Huntington disease came to public attention in the 1940s when the well-known folk singer Woody Guthrie began to show symptoms of this fatal genetic disorder. Huntington disease received notoriety again in the 1980s and early 1990s when researchers, including Dr. Nancy Wexler, hunted for and located the mutant gene that causes HD. Dr. Wexler caught the public's interest in part because she had a direct and personal concern with this genetic killer: her mother died of Huntington disease, so Dr. Wexler knew she was at risk.

HD is inherited as an autosomal dominant disorder. It is rare, occurring at a frequency of about 1/20,000 in Western countries and less often in Asia and elsewhere. The onset of symptoms generally occurs in adulthood, but the age varies among individuals and between generations of affected people. The disease involves neurological function, and early symptoms include twitchy muscles, awkwardness of movement, and memory dysfunction. Eventually symptoms become severe, and death results. The gene is located on chromosome 4.

Figure 3-2 Myotonic Dystrophy (DM): Summary of Symptoms

Myotonic dystrophy is a fairly rare inherited human disorder that occurs in 1/8000 Caucasians and even less frequently in other groups. DM shows a large degree of variability in the type and severity of symptoms. The age of onset may vary from one family member to another of those affected. In its mildest forms, DM leaves the individual asymptomatic until late in adulthood. Then it may show up only as cataracts on the eyes, which affect vision. Because cataracts are not uncommon in elderly people, many individuals with extremely mild DM symptoms may not realize they have inherited this disorder. (Conversely, just because a relative of yours has had cataracts, do not assume that DM occurs in your family.)

More serious symptoms include muscle abnormalities such as a breakdown of muscle tissue and the inability to relax a muscle after it has been contracted. Other symptoms involve damage to the heart or the sexual organs (gonads). Some individuals who have inherited DM show mental retardation as children. A less severe form results in unusual drowsiness and inattentiveness in adults.

Myotonic dystrophy is inherited as an autosomal dominant disorder. The gene is located on chromosome 19.

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Dr. B: "(Laughing) Perhaps. But you haven't mentioned a different publication from that year, the one by that geneticist Penrose. He mentions Bell's work and reports from other geneticists, but he points out that simple Mendelian inheritance of a dominant trait won't result in the increasing problems of the disease in children and grandchildren of someone who has the disease gene."

Dr. A: "Then how do you explain the observed anticipation?"

Dr. B: "I don't, at least, not yet. It may be an error in observation. Besides, I would need more data."

References:

J. Bell (1947). Dystrophia myotonica and allied disease. in *The Treasury of Human Inheritance IV. Nervous diseases and muscular dystrophies*, vol 5, p. 343; and L.S. Penrose (1947). The problem of anticipation in pedigrees of dystrophia myotonica. *Annals of Eugenics* 14:125-132.

Think about the dialogue as you respond to these questions.

a. What is genetic anticipation?

The term refers to a pattern of earlier onset and more severe symptoms of a genetic disorder in later generations.

b. Why does Dr. B. want more data?

The sampling error decreases in a study when there are more data. (Remind students of their coin-toss experiment in Activity 2.) In addition, multiple lines of evidence either strengthen an explanation or show that it is inadequate or inaccurate. Either way, more data generally help. The anecdotal case discussed in the fictitious dialogue would have had less significance than the research publications to which Dr. A and Dr. B. refer, because these publications are based on more than one case.

c. Dr. B. refers to "an error in observation." How might such an error arise? What could be done about it?

If a physician thinks genetic anticipation occurs, he or she might *look* for it in at-risk offspring, thus seeing disease symptoms earlier than might otherwise be the case. This pattern could result in a false impression of the earlier onset of symptoms in children and grandchildren of an affected individual. A controlled case study would provide for offspring to be examined at the same ages in a large number of families. In addition, the study would need to be done by more than one physician, perhaps with a "blind" study, where the physicians examine patients without being told what disease is suspected.

d. What have you learned about dominant inheritance? Why is genetic anticipation *not* explained by this genetic concept?

Dominant inheritance predicts that one-half of the offspring of affected parents will be affected and the presence of one allele will result in phenotypic expression. The concept of dominant inheritance does *not* explain genetic anticipation because this traditional concept does not include any mechanism that would result in affected individuals in different generations manifesting the disorder at an earlier age, or with more severe symptoms, than did their ancestors.

e. What else could be done to solve this mystery?

Collect additional data, analyze patterns in more families to see whether there is consistent evidence for genetic anticipation. Urge students to articulate what patterns they might look for in the data here and with data in the next part of the activity. These patterns include the age at which symptoms appear, the age of death, and the degree of severity for HD and DM.

Part II: Gathering Clues to the Mystery

Distribute the first set of HD clues (from Copymaster 3-1) among the teams.

The year is 1977. **You have collected interview data from many of the members of Allen's family. Use what you know from the dialogue and from this new case-history information to answer the Challenge Questions in Figure 3-3.**

1977

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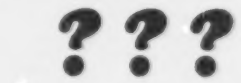
Figure 3-3 Challenge Questions



Scientists had to think about genetic anticipation in several steps. They needed to break the problem into addressable questions.

- What evidence do you have to support or refute the existence of genetic anticipation?
- Do you have evidence that supports a possible explanation for the genetic mechanism that causes anticipation? If yes, explain.

2. Each team has different clues obtained from case histories. You only have a few minutes to consider your team's clues before you pool your information with that from other teams.

Prompt your students to suggest building a pedigree before you give each team the template for the HD pedigree (Copymaster 3-3). Give students only about two minutes to see how their clues fit together before you begin the team jigsaw to build the whole pedigree.

3. Follow your teacher's instructions about how to report your preliminary findings.

Devise a way to display the clues from all teams, assembled in a jigsaw fashion. You may write on the board or on an overhead transparency of the pedigree template (Copymaster 3-3). Remember that the clues for each team represent one section of the pedigree. Notice that the individual from the dialogue, Allen, is marked on the template. Ask students to volunteer information about the identities and health data for each family member, perhaps starting with someone directly related to Allen. For example, you could point to Allen's twin daughters and ask, "Does any team have information about these family members?" Make this step very quick and fun. You may find it most effective to have teams volunteer information in an informal, unstructured way.

If you prefer a more orderly approach (and less noise), try calling on students by teams to ask for specific information. When the pedigree is complete, move to the next step.

4. What does this evidence tell you about the Challenge Questions in Figure 3-3 (if anything)?

Students should be able to cite evidence for the *existence* of genetic anticipation, they do not yet have evidence for the *causal mechanism*. If students have difficulty doing this, use some intermediate questions to help them structure their thinking. For example, ask them to compare the health and lifespan of Martha, her son Allen, and her grandson Andrew, paying particular attention to their ages when symptoms appear.

Distribute the article from Copymaster 3-4 and the HD molecular clues from Copymaster 3-2. Each team will have one complete set of these clues.

Now the year is 1997. **Molecular biologists have devised a test to identify the mutant gene for HD and to determine some of its special properties. In addition, many of the family members have had the test; in some cases blood samples stored from older, deceased members were tested. Your teacher will supply you with an article that describes the new molecular test for HD and the results of this test when performed on the members of Allen's family.**

5. Read the article and record the information from the HD molecular clues on your HD pedigree. Report this information to the class when your teacher instructs you to do so.

Give students a few minutes to read the article and record the information on their pedigrees, then quickly have the class volunteer the molecular data to add to the class pedigree.

6. Why does each person tested have *two* repeat numbers?

There are two copies of each chromosome and consequently two copies of the gene being tested.

7. Using this new evidence, once again address the Challenge Questions in Figure 3-3.

Now students have a new line of evidence to support the existence of genetic anticipation, plus evidence

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to suggest a possible mechanism (expansion of trinucleotide repeats). You could help stimulate the students' thinking by asking a question such as, "Why might the results of his parents' test cause Evan to decide against being tested?" (The parents have only a few trinucleotide repeats in the gene associated with HD.)

Challenge Questions (from Figure 3-3)

- *What evidence do you have to support or refute the existence of genetic anticipation?*

There is evidence to support the existence of genetic anticipation. The pattern of disease corresponds to the number of CAG repeats, and the number of repeats increases in some individuals in later generations. For example, in the HD pedigree, Allen has 46 repeats in the mutant copy of the mutant HD gene, and he dies of Huntington disease. Linda, his wife, has only 22 copies of the repeats at most, and she does not develop the disease. Their oldest child, Andrew, dies of Huntington disease at an even earlier age than did his father, while a second child, Debbie, does not have the disease well past the age at which Allen became ill with HD. Andrew has 69 repeats in a copy of the mutant HD gene; Debbie has, at most, 15 CAG repeats associated with the mutant HD gene. Students may provide many other examples.

- *Do you have evidence that supports a possible explanation for the genetic mechanism that causes anticipation? If yes, explain.*

Yes. The instability of trinucleotide repeats from one generation to the next suggests the molecular basis for the pattern of genetic anticipation.

8. One of the strengths of a good scientific explanation is that it is supported by multiple lines of evidence. Use a set of clues for a different family to look for additional evidence that supports your answers to the preceding questions.

Distribute a complete set of the DM familial health clues (part A from Copymaster 3-5) and a copy of the template for the DM pedigree (Copymaster 3-6) to each team. You may want to have teams race to see which one can complete the pedigree first, or assign the pedigree as homework, giving each student a copy of the clues and the template. After students set up the pedigree, distribute the molecular clues for myotonic dystrophy (part B from Copymaster 3-5) to each team. Give each team time to organize its clues before asking for the students' response to the challenge questions.

The pedigree for myotonic dystrophy provides additional evidence to support the existence of genetic anticipation, plus additional evidence to support the explanation that unstable trinucleotide repeats in the mutant gene are part of the mechanism underlying genetic anticipation. Emphasize this important aspect of scientific methods by asking students how the DM data affect their explanation of anticipation.

Part IV: Discovering the History of Genetic Anticipation

This section is optional, but it provides a rich context for the history of our understanding of genetic anticipation. As such, the examples show many features of the nature of science, including how new work builds on old work, and the need for sufficient evidence to support a new explanation. (Sufficient evidence is more than limited anecdotal evidence or unsubstantiated ideas offered by an individual scientist who has considerable status in the scientific community.)

The sequence of discovery demonstrated by the clues you used reflects the history of discovery about genetic anticipation. Use the brief scenes (vignettes) that your teacher will give you to build a more complete picture of the history of discovery about HD and genetic anticipation. As you read, try to determine at what point in the sequence the opening dialogue between the fictitious Drs. A. and B. might have taken place. What additional vignettes might follow these in the future?

Distribute one copy of the vignettes to each team (Copymaster 3-8).

9. Read the vignettes and discuss with your teammates what they tell you about the history of our understanding of HD.

10. As a team, draw up a brief outline of the history of discovery about HD.

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11. Individually, write a new vignette that represents what you predict may be the next level of discovery about HD.

12. After you complete the vignette, explain the aspects of science on which you based your predictions.

Analysis

1. What is the relationship between the number of trinucleotide repeats in the mutant HD or DM gene and the resulting phenotype?

There is a threshold number in the case of HD. Individuals who have about 39 or more repeats almost certainly develop the disease unless they die from some other cause first. Usually there are not more than 120 repeats in the HD mutation. In the case of DM, the threshold number is about 50-80 for mild symptoms. Those who have severe symptoms of DM have inherited hundreds to more than 2,000 trinucleotide repeats in their mutant DM gene. The more repeats above the threshold number, the more likely the disease phenotype will develop, the more likely the onset will be early, and the more likely the affected person will display more severe symptoms.

2. How does what you know about genetic anticipation contrast with the traditional, Mendelian view of autosomal dominant inheritance?

The traditional understanding of autosomal dominant inheritance includes no assumptions about the ability of an allele to change its size and does not, therefore, identify a mechanism that explains genetic anticipation.

3. How have you used the methods of science in this activity?

Sample student responses include:

- We collected and analyzed data.
- We reviewed earlier work done on this problem.
- We made our data and conclusions available for analysis by others.
- We assumed that these observations are explainable in terms of natural causes.

You may want to have students add to or consult the NMS poster.

4. Write a vignette (brief scene or part of a story) about the future health of Peter, Cathy, and Sean. Use your case-history data and the article you read to support your description.

Student responses may be more creative, but the basic information should show the following: If Peter has inherited HD from his father, his symptoms may occur at an early age, because his father had a large number of repeats. The trinucleotide number could, however, decrease. DNA analysis would determine Peter's number of repeats and provide a better prediction. Cathy is not likely to have HD because her mother, Paula, has at most only 13 repeats, and at that number the gene is generally stable. In the DM family, severe symptoms should already be apparent for Sean because he has a large number of repeats.

Activity 4
Should Teenagers Be Tested for the Mutant HD Gene?

NMS Concepts

New discoveries in science and new technologies sometimes raise difficult ethical questions.

Genetics Concepts

Genetic anticipation in Huntington disease correlates to the number of unstable trinucleotide repeats; genetic testing for Huntington disease can predict what is likely to happen to a person with the disease.

Focus

This activity challenges students to explore a policy commonly followed by genetic-testing centers to withhold genetic tests for Huntington disease (HD) from asymptomatic patients under the age of 18. Students will use their prior knowledge about HD and reflect on their own decision-making capabilities as they analyze a policy that raises significant ethical issues.

Objectives

As the students complete this activity, they should

1. revisit the scientific and clinical implications of HD;
2. gather and evaluate information and make and analyze arguments as tools for ethical inquiry;
3. take and defend a position on whether to recommend that genetic-testing centers offer genetic testing for HD to asymptomatic teenagers; and
4. state alternative viewpoints on an accepted policy among genetic-testing centers.

Estimated Time

30–45 minutes plus homework

This activity can be taught as a fairly brief, focused discussion of ethical issues; the estimated classroom time of 30–45 minutes reflects this approach. The activity has the potential, however, to generate much deeper discussion. You may want to explore in more detail some of the concerns that students raise.

Preparation and Materials

You will need to provide the following:

- 1 copy per student of Copymaster 4-1, *Worksheet for a Discussion about Policy*

If you have not taught Activity 3 prior to beginning this activity, you may want to review some characteristics of HD, including the role of trinucleotide repeat expansion. For details, see Activity 3 and page 43 in Section V of the *Overview for Teachers*. If you plan to teach Activities 3 and 4, we strongly recommend presenting them in numerical order.

Copymasters used in this activity

Copymaster 4-1

Worksheet for a Discussion about Policy

Introduction

An important responsibility of the Human Genome Project (HGP) is to examine the effects of the project on individuals, communities, and society. Both major funding sources for the HGP (the United States Department of Energy [DOE] and the National Institutes of Health [NIH]) provide resources to support the investigation of related issues. This component of the HGP is called ELSI (Ethical, Legal, and Social Implications; see Section IV in the *Overview for Teachers* for more information about ELSI). Activity 4 addresses ELSI issues connected with genetic testing and related specifically to analysis of trinucleotide repeats in Huntington disease.

Issues Associated with Genetic Testing: The decision for a health-care provider to conduct a genetic test is based on a variety of factors. Health-care professionals are trained to reduce risks to their patients, including psychosocial risks. Such risks are real in testing for the HD mutation. Anxiety and depression may arise in response to a positive test result. A similar issue received attention in the mid-1980s, when health-care professionals had to decide how to handle testing for exposure to the AIDS virus, HIV. At that point, the connection between a positive test for exposure to HIV and development of the fatal disease AIDS was not yet clear (although the correlation has since been established to the satisfaction of virtually all scientists). Keep in mind that there is a distinction between having the HD *gene* and having the HD *mutation*. (Everyone has the gene; it is the presence of a mutation in that gene that results in the genetic disorder known as Huntington disease.)

Other factors that a health-care provider considers when making a decision about genetic testing include the following questions:

- Can the disorder, once diagnosed, be treated?
- Does the patient exhibit symptoms, or is the order for a test based on family history alone?
- What is the balance of benefit versus harm brought about by knowledge of the test results?

The issue becomes even more complex when the patient to be tested is a minor, that is, under 18 years of age.

The request for a genetic test may come from the parents or from the minor. When the minor is an adolescent, the issue becomes particularly complicated because the patient may exhibit a considerable degree of autonomy regarding his or her health-care decisions. A report from the American Society of Human Genetics (ASHG) and the American College of Medical Genetics (ACMG), titled Points to Consider: Ethical, Legal, and Psychological Implications of Genetic Testing in Children and Adolescents, is a useful resource for teaching this activity (*Am. J. Hum. Genet.* 57:1233-1241, 1995). The report points out that in these cases "...the primary goal of genetic testing should be to promote the well-being of the child." The report also addresses the impact on family members. "Presymptomatic diagnosis in children also has the potential to alter the relationships that exist between parents and their offspring and among siblings." The child who tests positive may be overindulged or may be treated as a scapegoat. Both of these problems can occur, however, even in the absence of testing. The testing of a child (or indeed any other family member) also has implications for all members of the family. In some cases, this forewarning will be welcomed; in others, it may be unwanted. Genetic testing of a child will ease some aspects of uncertainty, but people differ greatly in their response to such news.

In the case of genetic testing for the Huntington mutation, most health-care providers and genetic testing centers adhere to a policy that denies tests to minors who do not exhibit symptoms. This denial extends to requests from the parents, who are the legal guardians of the child's health. The rationale for this policy is that HD generally occurs in the adult years (particularly during middle-age), and there is no treatment. For these reasons, there is no immediate, physical health benefit from a specific diagnosis based on genetic testing for a minor. The psychological effects can be mixed. While some individuals prefer the release from uncertainty, others could view a

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positive result as a death sentence and react in ways that are destructive to themselves or their families. Genetic testing requires informed consent, and some geneticists argue that this requirement automatically rules out children, and even teenagers, who generally are judged incapable of providing such consent. As the ASHG ACMG report makes clear, however, this view of minors is far too broad and may not be realistic. Some specialists are beginning to recognize that some adolescents and young children have sufficient autonomy in consent and decision-making, and the authors suggest that the desires of these youths should be taken into account. In any event, one must weigh the *balance* of potential harm and benefit.

The current policy is to delay the decision to test for the HD mutation until the individual is an adult and can make the decision, rather than letting parents remove this option by making the choice themselves. Note that a *change* in policy most likely would result in *parents* being permitted to make the decision, rather than leaving the decision to the minor in question. This situation is reflected in Step 2 of this activity. Either way, issues of ethical decision-making (discussed in the following paragraphs) will arise. To keep Activity 4 focused, we have structured it around our assumption that this change is the most likely alternative to the current policy. Other options for a new policy are worth considering, however. For example, the new policy could allow competent minors to make the choices, either as a general rule or in special cases. (See comments under Strategies for Teaching the Activity.)

Ethical Decision-making in the Classroom: Ethical decision-making is a complex process that includes many variables, but one can examine the process in concrete terms that teenagers can understand. Activity 4 involves students in a discussion of ethical issues surrounding a debate about a genetic-testing policy. Although this discussion is not a formal ethical analysis, it is grounded, in prominent ways, in the ethics of problem-solving. This activity raises two central issues: "prudential judgment" and "developmental autonomy." The former refers to the factors necessary for judging an issue wisely; the latter involves criteria for judging that someone is sufficiently capable of making his or her own decisions, independent of parents or guardians.

We use prudential judgments when our future interests are at risk in uncertain or unknown ways. Prudential judgments concern the probability that the events for which we are at risk will occur. Such judgments also weigh the benefits against the harms inherent in particular outcomes or consequences. Hopefully, the act of judgment is followed by choosing to pursue the option that, at least, minimizes harm and, at best, provides benefit. Prudential judgments do not necessarily involve situations with a "right" or "wrong" answer. They will exhibit variability by their very nature because they involve human values, probability, and relative risk. Prudential judgments can be made sloppily or rigorously. Rigorously made prudential judgments follow a process of intellectual discipline in which one weighs risks and benefits carefully. Sloppily made judgments are more likely to result in surprises, because the ramifications of a decision are not examined carefully beforehand. The ethical criteria one employs in this intellectual process will determine the quality of the judgments one makes.

Developmental autonomy, in the context of this activity, concerns the decision-making capacity of teenagers with regard to access to genetic information and the larger issue of whether a minor is able to make informed decisions about personal health and medical services. Elements of this ability include processing information, reasoning causally, assessing the worth of likely future events using value judgments that are based on facts and that have been well considered, expressing a preference in light of those judgments, carrying out preferences, and accepting responsibility for one's choice or action. A formal discussion of these issues is provided in the *Overview for Teachers* (Section IV; see especially pages 29-31).

Strategies for Teaching the Activity

As indicated in the Introduction, this activity is simplified because it chooses the *most likely* alternative to current policy (this alternative being that parents normally will decide for their children) and lets students compare that alternative to the current policy. This comparison begins in Step 2 of Part I of the activity. There are, however, many other interesting options, such as a change in policy that would put

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the burden of decision on the minor. To provide a more open-ended approach, you could ask students at Step 2 to decide whether the policy should change and, if so, to what alternative. Do not get into an involved discussion at this point. Just identify an alternative suggested by the class and then call for a vote based on the two options: to maintain the current policy or to change the policy to one suggested by the class. With this open-ended approach, the sample responses provided in Question 4a of the Annotated Student Material may change.

Please note that we refer to choices that involve children or their parents, but many of your students may live in households that do not have a traditional set of parents. A student, for example, may live with a single parent or with grandparents. Please be sensitive to these differences where possible.

The following aspects of prudential decision-making are important in the context of this activity. Consider the policy to deny genetic testing to asymptomatic teenagers who are at risk for HD. Is this policy unjustifiable because it prevents risks that prudent people could take for themselves? Is the policy justifiable because it protects the right of minors to make these decisions later in adulthood, rather than being superseded by parental authority? As you explore these issues, help your students to recognize that there is a wide range of prudential judgments, from those that are highly risk-averse to those that are much less so. You can do so by contrasting examples from each end of the spectrum.

The distinction between genetic testing for minors or adults also rests in part on developmental autonomy with regard to decision-making. Help students test their own developmental autonomy by using the debate in this activity. Students can record their responses on Copymaster 4-1. We provide some sample responses on the annotated version of Copymaster 4-1, page 117. Questions 1 and 2 of the Analysis also allude to developmental autonomy.

The following summary of this activity will give you a snapshot of the procedure.

Activity 4 at a Glance

Part I: **Identifying the Issue**
Students learn about an actual health-care policy that withholds genetic testing for asymptomatic teenagers who are at risk for HD. The students express their opinions about the policy by voting to retain it or amend it.

Part II: **Using Ethical Decision-making**
Students apply skills in ethical decision-making and analyze the topic in depth before they vote again.

Analysis: Students examine the usefulness of scientific evidence and look at other ethical issues related to new discoveries in genetics; they personalize their discussion of the policy on genetic testing.

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Annotated Student Material

Separate student pages contain the material shown in **bold** typeface.
Here, we provide an annotated version of student materials to help you conduct the activity.

How should you go about making good choices about important issues in life? Should you base your decisions on a whim, a coin toss, or a call to a psychic hot line? Or should you rely on well-informed, well-reasoned analysis? Scientific reasoning is a disciplined way to understand events in the natural world. Similarly, a discussion of ethical issues brings reason and discipline to decisions that involve preferences based on values. We draw our values from many sources, including history, law, religion, and family. Part of the task of ethics is to identify these values clearly and to show why others should regard them as important. A discussion of ethical issues may apply to what we do as individuals or to how public policy is made. In this activity, you will use the principles of sound decision-making and ethics to decide whether a policy that excludes teenagers from genetic testing is a good public policy.

PROCEDURE

Part I: Identifying the Issue

1. **People often express their opinions or concerns through a letter to the editor of a newspaper. Read the letter shown in Figure 4-1.**

If students have completed Activity 3, they will guess that the letter is from Jean Wu, and that it refers to her husband, Nathaniel, and son, Peter. Because the letter is personal, she likely would omit their names and her surname.

2. **Assume that a change in policy would give *parents* the right to request an HD test for a person who is under 18 years of age. Decide whether you think the policy of not testing minors should stand or be changed. Register your vote when your teacher polls the class.**

Give students just enough time to read the letter, then restate the issue and call for a vote. Record the class poll "for" and "against" changing the policy.

Part II: Using Ethical Decision-making

3. **Form teams as directed by your teacher to conduct a discussion of the ethical issues in the letter. *Regardless of your personal opinion* on this issue, work with your team to draw up two lists of opposing ideas about this policy, using the worksheet provided by your teacher. In the left column, list reasons the current policy is good. In the right column, list reasons the policy should change or why the new policy is better. Record all of your team's ideas.**

Distribute Copymaster 4-1 to each student. Ask students to form teams of three or four. Have students discuss and record their reasons. Allow about 10 minutes to complete this exercise.

4. **Present your team's ideas to the class. Add notes to your own worksheet of new ideas that arise during the discussion with other teams.**

Record the students' responses on the chalkboard, on a transparency, or on a large sheet of paper. You may want to remind students that HD is a late-onset condition; teenagers, therefore, may not show symptoms even if they will develop the disease later on. Thus, they could make a decision about testing after they are adults. In addition, there is currently no treatment for HD even though the disorder can be diagnosed; there is considerable emotional stress associated with testing. Future research, however, may find therapies that help.

The following questions may help you guide this discussion. *Be certain to leave enough time for a second vote.*

a. *Reflect on the reasons the class offered for making a decision about testing for HD. What major*

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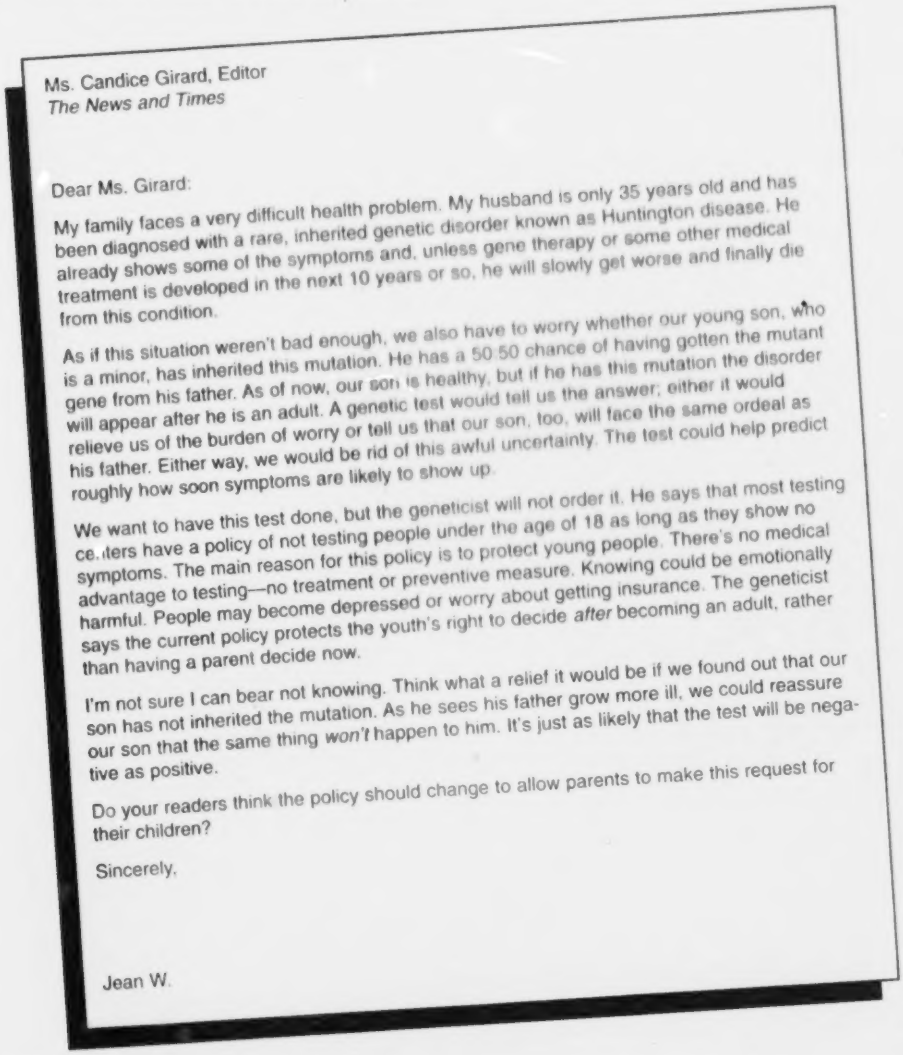
Figure 4-1 Letter to the editor of a city newspaper



Ms. Candice Girard, Editor
The News and Times

Dear Ms. Girard:

My family faces a very difficult health problem. My husband is only 35 years old and has been diagnosed with a rare, inherited genetic disorder known as Huntington disease. He already shows some of the symptoms and, unless gene therapy or some other medical treatment is developed in the next 10 years or so, he will slowly get worse and finally die from this condition.

As if this situation weren't bad enough, we also have to worry whether our young son, who is a minor, has inherited this mutation. He has a 50:50 chance of having gotten the mutant gene from his father. As of now, our son is healthy, but if he has this mutation the disorder will appear after he is an adult. A genetic test would tell us the answer; either it would relieve us of the burden of worry or tell us that our son, too, will face the same ordeal as his father. Either way, we would be rid of this awful uncertainty. The test could help predict roughly how soon symptoms are likely to show up.

We want to have this test done, but the geneticist will not order it. He says that most testing centers have a policy of not testing people under the age of 18 as long as they show no symptoms. The main reason for this policy is to protect young people. There's no medical advantage to testing—no treatment or preventive measure. Knowing could be emotionally harmful. People may become depressed or worry about getting insurance. The geneticist says the current policy protects the youth's right to decide *after* becoming an adult, rather than having a parent decide now.

I'm not sure I can bear not knowing. Think what a relief it would be if we found out that our son has not inherited the mutation. As he sees his father grow more ill, we could reassure our son that the same thing *won't* happen to him. It's just as likely that the test will be negative as positive.

Do your readers think the policy should change to allow parents to make this request for their children?

Sincerely,

Jean W.

ethical issues or common areas of concern did the class identify?

You may find that this case raises at least two areas of concern, the first involving prudential decision-making and the second involving developmental autonomy (for example, right to know, competence, and maturity). The Introduction to this activity reviews these topics. Sample responses are provided in Figure T4-1, the annotated version of Copymaster 4-1. Students may express these same ideas in much simpler language. Responses will vary depending on what option you and your class chose for the policy change (parents decide, or minors decide, or some other plan).

b. *How would retaining the current policy help or injure the teenagers in question, or their family members? How would changing the policy help or injure the teenagers or their family members? How should we evaluate those outcomes?*

Ask students to defend their selection.

Note from the field test: Most field-test teachers found that a few students change their votes, which shows the importance of the discussion.

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Figure T4-1 Annotated Worksheet for a Discussion about Policy

Current policy: To withhold genetic testing for Huntington disease for asymptomatic minors.	
Reasons to maintain policy	**Reasons to change policy**
(Prudential Judgments)	
Bad events could result (such as depression, divorce, or loss of employment).	Bad events do not necessarily follow.
Bad events should be avoided even if the risks are low.	We have an obligation to know about our genes for the sake of future generations.
Testing won't change the outcome.	Parents and teenagers have a right to know.
There is no treatment at present.	Teenagers may find out that they tested negative for HD.
Parents might not want to pay for college.	If tested, teenagers might choose to live differently, knowing they will become ill later.
Testing later may be done in a context of (future) treatment.	Knowledge of one's genetic status can help with planning, such as whether to develop relationships.
Testing could adversely affect one's status as an insurance carrier.	
(Developmental Autonomy)	
Many teenagers cannot make informed decisions.	Many teenagers can make informed decisions.
The majority of teenagers are neither cognitively nor emotionally mature.	Some teenagers can understand genetic causal relations, if they choose to learn.
Genetic causality is too complex for teenagers to understand.	Early onset could mean that symptoms will appear only a few years after the age of consent. Knowing sooner could give the teenager more time to make important decisions
Some teenagers are self-centered and ignore consequences to others.	There are some teenagers who are cognitively and emotionally mature.
Many teenagers have values that are too unstable.	Knowing could affect other children in the family or close relatives, perhaps reducing worry.
Teenagers found to have the mutant HD gene might not choose to go to college or to seek employment.	
Knowing could adversely affect other children in the family who are too young to deal with the problem.	

5. Consider the discussion of ethical issues performed by the class and vote again: Is the current policy good and worth maintaining, or should it be changed so that parents of minors at risk for HD can have their children tested?

Point out to students the important difference between deciding for or against a policy and deciding whether *one actually would agree to be tested*. An individual can vote to allow testing and still elect not to be tested personally. Take a vote to establish what most students think should be done.

Even if you have taught the activity as written, you may want to challenge students with a question such as, "In what other ways could the policy be changed?"

Analysis

1. Given that there is no treatment at present for HD, how does acquiring scientific evidence about the presence or absence of the HD mutation (from a genetic test) change the discussion of the issue?

Fears or concerns about developing HD will be based on family history. If this case-history information is thorough and coupled with an informed scientific

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understanding, speculation is limited to a consideration of the odds. For example, a child has a 50:50 chance of inheriting the mutation if one parent is known to be affected; the issue is less clear if a grandparent is known to have HD. With the results of the genetic test, *direct evidence* is available, and the issue is reduced to one of two possibilities: (a) the individual has not inherited the mutation and will not develop HD; or (b) the individual has the mutation and, short of death by another means or the advent of a medical treatment, the individual almost certainly will develop HD. The number of trinucleotide repeats present in the mutant gene also helps to predict the age of onset. (See Activity 3 and Section V of the *Overview for Teachers* for more detail about this form of genetic evidence.)

2. What additional social and ethical issues might new knowledge in genetics raise?

Responses will vary, but may include the following:

- How much information should we be allowed to have access to and when? For example, should we regulate access to genetic information by schools, insurance companies, or by agencies of the government?
- What constitutes genetic discrimination?
- How should we respond to pressure imposed for testing by families, employers, or institutions?
- Who pays for predictive testing?
- How much funding should we devote to developing genetic tests and treatments?
- If you are found to carry a disease-related gene but are asymptomatic, are you sick? What would others (your family, your teacher, your employer, your health-insurance company) think about your state of health?
- What issues concerning reproductive decision-making does new knowledge in genetics raise?

3. As a homework assignment, write a response to Jean W.'s letter. You might let her know whether *you* would choose to be tested, and why. In your letter, describe what scientific evidence from a genetic test will tell you and how that information affects your choice. In addition, show how the discussion of ethical issues that your class conducted has influenced your ideas.

Student responses should reflect an understanding of the scientific significance of testing, an understanding of the behavior of the HD allele, and a well-reasoned, clearly supported, personal opinion about testing.

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Activity 5
What Do We Know? How Do We Know It?

NMS Concepts

This activity reviews all concepts addressed in the module, with particular emphasis on the following:

- A scientifically valid explanation contains supporting evidence, is well reasoned, is based on a sound premise, is testable, and demonstrates a causal relationship.
- An explanation can be tested for scientific validity.
- The scientific enterprise reflects the culture in which it is embedded and may raise issues of ethical concern.
- Much of scientific knowledge is long-lasting, but new explanations arise in response to new evidence.
- Scientific knowledge and skill are relevant to nonscientists.

Genetics Concepts

This activity reviews traditional genetics and some nontraditional explanations of inheritance introduced in the module, including extranuclear (mitochondrial) inheritance, genetic anticipation, and instability of trinucleotide repeats.

Focus

Activity 5 serves three purposes: (1) it is a synthesis that helps students evaluate what they have learned in the module about the methods of science and about genetics; (2) it provides a bridge between these studies in the classroom and issues in the world outside of school; and (3) it provides an opportunity to assess student progress. Students examine popular claims that may be scientific or pseudoscientific and critique these claims for scientific validity. The last part of the activity assesses students' understanding of how science works, of genetics concepts, and of the cultural aspects of science. It also assesses the ability of individual students to evaluate popular claims for scientific validity.

Objectives

As students complete this activity, they should

1. review their understanding of genes and inheritance;
2. consider how and why genetics explanations change;
3. evaluate popular media topics for scientific validity; and
4. draw together their ideas about the nature and methods of science from throughout the module.

Estimated Time

One 50-minute class period, plus homework.

Preparation and Materials

Advance preparation: Several days before conducting the activity, ask students to find articles that make claims about popular science or pseudoscience topics that pique their curiosity. These articles should come from a variety of media sources, some reliable, some less so. Alternatively, you may want to supply a sample of publications (for example, local newspapers, *National Enquirer*, or *Discover*) or specific articles to ensure a good selection. Have students bring to class the articles or notes about the articles (if they were reported in nonprint sources). Encourage selection of diverse topics, such as reports of UFOs, crystal power, diet claims, or reports of medical treatments.

On the day of the activity, students will work in 4 teams. You will need to provide the following:

- 4 large sheets of paper (for charts, plus masking tape to post them)
- markers of 4 different colors (one color for each team)
- articles about popular claims that the students or you supply (the source of the articles must be indicated)

Before class, post the sheets of paper where students can see them and can write on them. Allow sufficient room around each chart so that a team can gather when the students are listing their ideas.

Introduction

> *"Science is a way to call the bluff of those who only pretend to knowledge. It is a bulwark against mysticism, against superstition, against religion misapplied to where it has no business being. If we're true to its values, it can tell us when we're being lied to."*
>
> *"Finding the occasional straw of truth awash in a great ocean of confusion and bamboozle requires vigilance, dedication, and courage. But if we don't practice these tough habits of thought, we cannot hope to solve the truly serious problems that face us—and we risk becoming a nation of suckers, a world of suckers, up for grabs by the next charlatan who saunters along."*
>
> Carl Sagan,
> *The Demon-haunted World: Science as a Candle in the Dark*, New York: Random House, 1995.

Activities 1, 2, and 3 in this module emphasize that the principles of inheritance established by Mendel and other geneticists have proven remarkably durable for more than a century. Continued research in genetics builds on the robust foundation constructed by these early workers. In recent years, geneticists and molecular biologists have added enormous amounts of new knowledge to that foundation. For example, advances in molecular biology—which allow scientists to isolate, sequence, modify, and transfer DNA or RNA—have formed a powerful conduit between traditional genetics and biochemistry. Now, we can explain at a molecular level concepts such as mutation and linkage. By extending our knowledge to cover the complete genomes of several species, the Human Genome Project will enhance our understanding of basic genetics as it generates new technologies, provides insights into disease processes, sheds light on gene regulation, and increases our knowledge of evolution.

In light of these, and other, modern technologies and discoveries, the durability of fundamental principles established by Mendel and other early geneticists is even more remarkable. Their ideas have endured because these scientists held themselves accountable to the basic tenets of scientific exploration. Most notably, early geneticists insisted—as do all scientists—that new explanations be supported by evidence that meets the requirements of science. This closing activity of the module is intended to remind your students of these important aspects of science.

Although some of your students may someday become physicians, genetic counselors, or research geneticists, not all will have a direct need for sophisticated knowledge of genetics. They *all*, however, will need to understand and apply the methods of science as they interpret news reports, listen to advice from physicians, or make decisions about public policy.

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This activity asks students to demonstrate their understanding of the methods of science by challenging them to critique media reports of popular topics that either mimic science or are scientific. Note in particular the issue raised by the discussion question at the end of Part I of the Analysis. If scientific explanations were voted upon, they would no longer count as science, and the corpus of scientific knowledge would be subject to the whims of politics and popularity. We recommend an editorial published in *The American Biology Teacher* titled "Voting in Science: Raise Your Hand If You Want Humans to Have 48 Chromosomes" (J.D. McInerney and R. Moore, *ABT* 55(3), March 1993, pp. 132-133). Your students may enjoy reading it as a follow-up to this last activity in the module. Even reading the title to students could challenge them to think about the distinction between voting on an issue in a club or a political setting versus voting on results to establish scientific outcomes. (The funding of scientific research *is* somewhat subject to the whims of politics. That process is different, however, from subjecting scientific knowledge *itself* to acceptance or rejection on the basis of politics or popularity.)

History records two particularly significant episodes where voting, in a sense, influenced the corpus of scientific knowledge, neither to beneficial effect. In the seventeenth century, the Catholic Church had decreed that the biblical account of the nature of the heavens, an account that presented Earth as the center of the universe, was the inerrant word of God and, as such, not open to question. The great astronomer Galileo had data to the contrary, but the Church had the power, including the power of life and death, and thus its "vote" prevailed.

From the late 1940s through the mid-1960s, the unfounded, Lamarckian views of Trofim Lysenko held sway over Soviet genetics, indeed, all of Soviet biology. Lysenko's unsupported belief in the inheritance of acquired characteristics appealed to Stalin's views of a society that could be molded into a Communist collective. Lysenkoist views were forced upon all Soviet biologists and those biologists in countries that were under Soviet domination. As genetics and molecular biology were exploding in the West, the Soviet government turned its back on biology and embraced ideology. Western journals were forbidden or severely censored, and Soviet geneticists who refused to adhere to Lysenko's views were stripped of their positions. Some died in labor camps. The impact of this perversion of science extended beyond the scientific community. Because the Soviet five-year agricultural plans were derived from Lysenko's misguided views of heredity, they were doomed to fail. Some political historians believe that the collapse of Soviet agriculture ultimately led to the downfall of Nikita Khrushchev, Soviet premier from 1958 to 1964.

This activity provides students with a chance to place their understanding of the nature and methods of science into a cultural setting through the analysis of science in the popular media. In doing so, students cement their own understanding of the requirements of science and exercise their ability to think critically and make informed decisions.

Strategies for Teaching the Activity

Begin by telling students that this activity brings the module to a close by asking them to evaluate what they have learned and to use that new knowledge to analyze current issues of their choice. Students likely will find the popular articles engaging. Note that this activity works best when the rotation from chart to chart is crisp and quick. The goal is to generate lots of information in a short time, leaving plenty of time to analyze it. Students also have a sense of ownership because they select the popular media topics to be critiqued.

It is critical to keep this discussion focused on criteria for a good *scientific* explanation. The discussion should not be an emotional exchange of unsupported opinions, because then it only will model shared ignorance. The important issue is how to judge the scientific validity of a claim based on the information available. Some popular claims, such as the effect of garlic on fighting various infections, may be valid but reported in an unreliable way. For example, if a report makes extravagant claims for the healing power of garlic without providing any scientific evidence, the source is not reliable and students should not conclude that the claim has been shown to be valid. You could ask students what is missing in these situations (such as

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scientific tests, extensive observations, or reasoning about how a process takes place). In many cases, students could pursue this missing information in more reliable sources.

Use the Assessment to evaluate different aspects of student learning. Question 2b in the Assessment should help students see that scientific knowledge continues to grow with new work building on old. Question 3 is very open-ended; it provides a chance for students to see the influence of society in science and vice versa. Finally, the exercise in Question 4 provides an opportunity to test each student's ability to use the methods of science to critique reports encountered in the popular media. This performance assessment mimics real-life needs for scientific understanding.

The following summary provides a snapshot of the activity.

Activity 5 at a Glance

Part I: **Critique of popular media topics**
Teams work in carousel fashion to list examples and evaluate them for scientific merit.

Part II: **Analysis**
The class discusses the merits of popular media topics and considers how science applies to their own lives.

Part III: **Assessment**
Students review what they have learned about how science works and about lasting and new explanations in genetics. They apply their skills individually to evaluate popular media topics.

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Annotated Student Material

Separate student pages contain the material shown in **bold** typeface.
Here, we provide an annotated version of student materials to help you conduct the activity.

"They say getting too much sun can give you cancer."

Who are "they"? Should you believe what "they" say, and, if so, should you change your behavior in any way?

All of us must assume responsibility for making decisions that affect us and others, but this responsibility does not guarantee that we will make good decisions. That skill requires lots of practice and careful reasoning, and it requires intelligent analysis of information. For health-related comments, such as the preceding quote, you should consider the scientific validity of the statement to determine whether you think the statement is reliable. Even if you decide that it is reliable, the choice of what to do about it still remains yours. (Is having a tan or relaxing in the sunlight worth the risk of getting skin cancer? How can you reduce the risk?) Whatever you decide, the ability to determine the scientific validity of a popular claim is a valuable skill for any person.

As you work through this last activity, you will evaluate what you have learned in the previous activities.

PROCEDURE

Part I: Critique of Popular Media Topics

You are going to critique claims from the popular press for their scientific validity.

1. **Recall from the previous activities the requirements of a good scientific explanation and list them.**

Spend one or two minutes polling students to make a collective class list. See Section III of the *Overview for Teachers* for a detailed discussion.

2. **Join your team and look at the articles the team members have collected. Choose one to present to the class. Discuss the reasons the article gives (if any) to support the claim being reported. (Be prepared to list the idea from the article and to give supporting evidence, if any, on a chart in the classroom. You have 5-10 minutes to prepare.)**

You may let students work from articles they bring to class, or you may want to provide a collection of articles yourself. To avoid redundancy on the charts, you can circulate during the preparation time and encourage students not to pick similar topics.

Note from the field test: Some students had difficulty looking for supporting evidence and acknowledging sources, such as a reference to a report in a refereed technical journal. Offer helpful suggestions, but keep the activity moving quickly. Omissions or weaknesses in understanding can be addressed comfortably in Part II, the Analysis.

3. **When your teacher gives the signal, move with your team to one chart and quickly list the claim from your team's article and indicate the source. Next show *why* this claim is supposed to be correct, according to the article. Spend only 2 minutes at this task.**

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Time the steps and stop each team after two minutes. Next, have teams quickly rotate to the next chart.

4. Move with your team to the next chart. Read the ideas listed by the previous team and critique this claim for its scientific validity. You have 3 minutes.

Stop the task at three minutes. Note that a team's comments can be identified by the color of its marking pen.

Part II: Analysis

Respond to the following questions as the class discusses the charts.

This discussion should *not* be an emotional exchange of opinions and beliefs. Instead, it should model a scientific analysis. The task is not to determine which students value each claim, but rather to evaluate the potential scientific validity of each claim. First, help students decide whether the claim is addressable by science or remains in the realm of untestable belief, religion, or other nonscientific ways of knowing. If a claim is testable scientifically, students should determine the weight of evidence, if any is available. The following questions may guide the discussion.

1. What is the difference between a belief and an explanation that meets the requirements of science?

This distinction is important for your students. Encourage them to see that some ideas, such as creationism, the use of Tarot cards, or other means of fortune-telling, may appeal to people emotionally and thus may encourage *belief*. Such beliefs, however, are based on faith, or belief in supernatural events, or on revealed knowledge; they are not based on reliable, scientific evidence. Such beliefs absolutely *do not* meet the requirements of scientific validity and thus are not taught as a part of science or recognized as legitimate subjects for scientific research. The question of an individual's belief in such topics, particularly religious subjects, is a matter of personal choice, completely external to a study of, and respect for, scientific knowledge. If any students have listed creationism as a science-based claim, this discussion may provide an opportunity for you to help the class understand that evolution is a scientifically valid explanation of biological change that is fully accepted by the scientific community, while creationism is not. Ongoing scientific debates about some of the subtleties of evolutionary process do *not* constitute any fundamental disagreement about the validity of evolution itself. The issue in a biology class is not whether a student should believe in creationism or whether it is "right or wrong"; the issue is that it is *not* supported by scientific evidence and thus is not a scientific explanation. Evolution is well-supported scientifically and is accepted as a scientific explanation; therefore it is suitable for study in a biology class.

You also may encounter concern about the term "theory." Students frequently misunderstand the meaning of this word in a scientific setting. Students may think a theory is a "guess." In informal use, one may hear an exchange such as this: "In theory, I was going to win the lottery." This lighthearted use of the word "theory" may leave students with the incorrect idea that a theory is an unfounded speculation. In science, a theory is a well-supported conceptual framework that explains a large number of observations about the natural world. Scientific theories also have predictive power, that is, they can help to predict the occurrence of natural phenomena. Chromosome theory, for example, predicts the occurrence of Mendelian ratios. Students generally accept atomic theory and chromosome theory without discomfort. The theory of evolution is no different in its scientific validity, although often it is singled out as a topic of concern because it conflicts with the religious beliefs of some people. Evolution theory is a well-reasoned scientific explanation that is supported by an overwhelming and ever-growing body of evidence as diverse as the fossil record or molecular experiments that demonstrate selection. (See Section III of the *Overview for Teachers* for more discussion of the use of scientific evidence to address scientific explanations.)

Many popular beliefs persist because it is easy to be intellectually lazy. If it is not easy to demand and locate supporting or refuting evidence, people may tend to follow the easier path and respond based on a whim rather than evidence. In addition, some people embrace unsubstantiated explanations

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simply because they feel better doing so—they find comfort in their beliefs. It is extremely important that students learn to distinguish well-reasoned, scientifically justified explanations from those that are rooted in unsupported assertions.

2. Based on the information presented on the charts, are any of the claims scientifically valid?

Students will offer a variety of opinions about which topics are scientifically sound and which are not.

3. How could your actions be influenced by knowing whether a claim is scientifically valid?

A student who understands the criteria for a scientifically valid claim may be less likely to be swayed by false claims that appear in the media or that have general public currency. The choice to buy certain over-the-counter medications, for example, might be influenced by assessing the efficacy of these products. Some topics, such as religious beliefs, fall outside the reach of science and should not be treated as scientific explanations.

4. Many health or science claims have significance in society because they are popular; that is, they have emotional appeal for many people. How would the work of scientists be different if scientific explanations were *voted upon for popularity* rather than held up to the scientific standards discussed in this module?

This question may provoke considerable discussion; if so, judge whether it is worth taking the time to pursue it. At this point, you could introduce the editorial cited on p. 121 ("Voting in Science: Raise Your Hand If You Want Humans to Have 48 Chromosomes").

You might want to close the module with a final look at the NMS poster.

Part III: Assessment

Respond to the following questions or assignments according to your teacher's instructions.

Students can be assessed individually or as a team, using written or oral responses.

1. Recall your experiences from the module as you answer the following questions:

a. What does science try to do?

b. How do we know that our scientific explanations are on the right track?

c. What counts as evidence in science?

d. What makes science objective?

e. How and why does scientific knowledge change?

f. What is the difference between pseudoscience and science?

This material is based on Section III of the *Overview for Teachers*. That section may help you evaluate student responses.

2. The previous activities used genetics examples to show how science works.

a. What genetics concepts did you discuss in this module?

Traditional genetics concepts are presented as milestone explanations in Activity 1. Expect students to list many of those or similar concepts. Figure 12 on page 36 of the *Overview for Teachers* also summarizes traditional concepts. Students also should list some new genetics concepts if they have used Activity 2 or Activity 3. Samples of how students might state these concepts follow:

- Some genetic information is inherited from the mother without equivalent information from the father.
- Offspring inherit some genes that are not part of the nuclear chromosomes.
- Some organelles have their own genes.
- Some genetic disorders get worse or show decreased age of onset in subsequent generations.
- Some genes change as they pass to the next generation.
- Mutant genes that cause Huntington disease and myotonic dystrophy have unstable trinucleotide repeats.
- The severity of HD and DM is related to the number of trinucleotide repeats in the mutant gene associated with each disorder.
- The number of repeats in mutant HD or DM

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genes helps predict whether an individual will develop the disease, the likely age of onset, and how severe the symptoms may be.

b. Were any of the genetics concepts you listed new to you? Identify them and indicate their relationship to earlier knowledge.

Concepts related to extranuclear (mitochondrial) inheritance or to genetic anticipation likely are new to students. These concepts connect to and extend existing knowledge. For example, explanations of anticipation also take into account what we know about dominant inheritance. Ideas such as these may be standard textbook material in the future because they have become so widely accepted that they are no longer novel. This process parallels the growth of scientific understanding.

3. How are science and society related? Give at least two examples.

Responses will vary. For example, scientific discoveries in genetics and other fields (such as deciphering the genetic code, identifying the function of specific genes, or developing the computer chip) actually change the way a society functions. These discoveries have altered diagnosis and treatment of disease, thus changing attitudes toward disease, and they have changed the way we store and use information in our business and leisure activities. Similarly, the concerns of a society help determine the path that research takes. Issues considered important by society are more likely to receive funding or to be brought to the attention of scientists. In some cases, society's interest takes the form of guidelines or restrictions in science, such as restrictions on the use of human subjects or safety precautions in laboratories that work with recombinant DNA.

4. Your job is to critique two claims that you see reported in popular media. One should be a science or health report that you consider to be scientifically reliable, and the other should be a claim that you think is not scientifically substantiated. (Remember, a claim could be based on a correct idea but reported poorly, making the *report* scientifically unsound.)

Assessment of the student responses should include these criteria:

- Is the critique clearly presented?
- Does the student recognize the role and significance of scientific evidence (or its lack)?
- Does the student recognize the importance of reliable reasoning and relevance of evidence?
- Does the student see the predictive power of scientific explanations?
- Does the student appreciate the power of multiple lines of evidence?
- Does the student distinguish between credible scientific evidence and unreliable information?
- Does the student distinguish between an explanation that is well-supported by scientific evidence and an opinion?
- Does the critique clearly cite the source of the reports?

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Special Copymasters for Classroom Activities

These copymasters are used as hand-outs or to make overhead transparencies.

Copymaster 1-1: Milestones in Understanding Genetics

Here, we omit numbers for milestones to avoid directing students to a particular sequence.

MILESTONES IN UNDERSTANDING GENETICS

Question:
Why do offspring resemble their parents?

Milestone Explanation:
Parents contribute genetic material to their offspring.

MILESTONES IN UNDERSTANDING GENETICS

Question:
How are traits distributed in offspring?

Milestone Explanation:
Alleles of one gene segregate in the formation of gametes.

(Reproductive cells [gametes] form during meiosis. Each gamete contains one allele from the pair of alleles present in the parent.)

MILESTONES IN UNDERSTANDING GENETICS

Question:
Where are genes located?

Milestone Explanation:
Genes are located on chromosomes.

(This idea is the chromosome theory of inheritance. In eukaryotic cells, genetic material is located in the nucleus in structures called chromosomes, for their dark-staining characteristic. The name comes from the Greek words *chroma* [color] and *soma* [body].)

MILESTONES IN UNDERSTANDING GENETICS

Question:
What determines the sex of an organism?

Milestone Explanation:
In most sexually reproducing organisms, special chromosomes determine sex.

(Humans have sex chromosomes, designated X and Y. The combination of sex chromosomes in an organism determines its sex.)

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Copymaster 1-1: Milestones in Understanding Genetics

Here, we omit numbers for milestones to avoid directing students to a particular sequence.

MILESTONES IN UNDERSTANDING GENETICS

Question:
Why do some traits occur together in offspring?

Milestone Explanation:
Some genes are located on the same chromosome (linkage).

MILESTONES IN UNDERSTANDING GENETICS

Question:
What molecular component in chromosomes carries genetic information?

Milestone Explanation:
DNA carries genetic information.

MILESTONES IN UNDERSTANDING GENETICS

Question:
How is the genetic information used to make proteins encoded?

Milestone Explanation:
In DNA, a triplet of nucleotide bases encodes each amino acid in the resultant protein.

MILESTONES IN UNDERSTANDING GENETICS

Question:
How does a new, heritable trait appear in a population?

Milestone Explanation:
Mutations change the structure of DNA in reproductive cells (gametes).

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Copymaster 1-2: Historic Sequence of Milestones

1. **Parents contribute genetic material to their offspring.**

2. **Alleles of one gene segregate in the formation of gametes.**

3. **Genes are located on chromosomes.**

4. **In most sexually reproducing organisms, special chromosomes determine sex.**

5. **Some genes are located on the same chromosome (linkage).**

6. **DNA carries genetic information.**

7. **In DNA, a triplet of nucleotide bases encodes each amino acid in the resultant protein.**

8. **Mutations change the structure of DNA in reproductive cells (gametes).**

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
Why do offspring resemble their parents?

Milestone Explanation:
Parents contribute genetic material to their offspring.

---

parents and offspring

Evidence A:
A scientist looked through a microscope at dividing cells in the tail fins of a salamander. As mitosis proceeded, she saw that chromosomes moved apart in equal numbers into the newly forming daughter cells. Other scientists observed this phenomenon in cells undergoing mitosis.

---

parents and offspring

Evidence B:
A scientist crossed pea plants and carefully recorded the appearance of certain traits in the offspring. When he crossed a strain that has only purple flowers with one that has only white flowers, the offspring always had purple flowers. When he crossed these offspring to produce the next generation, however, he saw both colors of flower in the new offspring in regular proportions.

This work was repeated later by other scientists who saw the same results.

---

parents and offspring

Evidence C:
Jorge noticed that a classmate, Susan, has curly hair. When he met her mother, he noticed that she also has curly hair.

---

parents and offspring

Evidence D:
Mendel said that characteristics of offspring likely come from something the offspring get from their parents.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
How are traits distributed in offspring?

Milestone Explanation:
Alleles of one gene segregate in the formation of gametes.

(Reproductive cells [gametes] form during meiosis. Each gamete contains one allele from the pair of alleles present in the parent.)

---

segregation

Evidence A:
People say that sons express the traits of the father, while daughters have all the mother's characteristics.

---

segregation

Evidence B:
Offspring in each generation are identical.

---

segregation

Evidence C:
Mendel speculated that traits are inherited based on discrete units of inheritance. He tested the law of segregation by observing height in several generations of pea plants. He saw a distribution of tall to dwarf in the F2 generation of 3:1. Then the F2 plants were fertilized with their own pollen (self-ed). Mendel found that the dwarf F2 plants produced dwarf F3 plants, but two-thirds of the tall F2 plants produced mixed offspring, dwarf and tall. This F3 test of segregation has been repeated many times with the same results.

---

segregation

Evidence D:
A scientist named W.S. Sutton observed chromosomes in cells undergoing meiosis. He noticed that the chromosomes behaved in a way that is consistent with Mendel's observations about inheritance patterns. Many other observations of meiosis by other scientists confirmed this behavior of chromosomes in the nucleus.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
Where are genes located?

Milestone Explanation:
Genes are located on chromosomes.

(This idea is the chromosome theory of inheritance. In eukaryotic cells, genetic material is located in the nucleus in structures called chromosomes, for their dark-staining characteristic. The name comes from the Greek words *chroma* [color] and *soma* [body].)

---

genes on chromosomes

Evidence A:
Using staining techniques and a microscope, C. Nageli discovered a set of structures in the nuclei of cells. Other scientists observed that these structures change and become visible with a microscope at certain times in the cell cycle. Years after Nageli's observation, a developmental biologist, W. Roux, observed these structures in the cell nucleus, and another scientist, W. Waldeyer, saw the structures and named them chromosomes.

---

genes on chromosomes

Evidence B:
A scientist named W.S. Sutton observed chromosomes in cells undergoing meiosis. He noticed that the chromosomes behaved in a way that is consistent with Mendel's observations about inheritance patterns. Many other observations of meiosis by other scientists confirmed this behavior of chromosomes in the nucleus.

---

genes on chromosomes

Evidence C:
A scientist, T. Boveri, showed that sea urchin embryos develop normally only when they have a full set of chromosomes. Embryos with more or fewer chromosomes than the normally observed number did not develop properly. Many other scientists have made the same observations in other organisms.

---

genes on chromosomes

Evidence D:
A professor at Harvard thinks that chromosomes contain genes.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
What determines the sex of an organism?

Milestone Explanation:
In most sexually reproducing organisms, special chromosomes determine sex.

(Humans have sex chromosomes, designated X and Y. The combination of sex chromosomes in an organism determines its sex.)

---

sex determination

Evidence A:
Many studies have shown that human females have two X chromosomes, and human males have one X chromosome and one Y chromosome. Patricia Jacobs and other scientists also showed that, although the normal human sex chromosome complement is XX or XY, other patterns do occur rarely. For instance, in humans, XXY individuals are male, and XO individuals are female.

---

sex determination

Evidence B:
During their lifetime, human males produce many sperm, but females produce only a few eggs. Many years of studies showed that females are born with all the egg cells they will ever have (although the eggs must mature individually during successive menstrual cycles). Males, however, produce millions of new sperm cells every few days until a very advanced age.

---

sex determination

Evidence C:
A scientist named C. E. McClung found that grasshoppers produce equal quantities of two different types of sperm, one of which contains an extra chromosome. Three years later, two other scientists, N. Stevens and E.B. Wilson, determined that female grasshoppers have two copies of one particular chromosome, whereas males have only one.

---

sex determination

Evidence D:
There is a saying that a pregnant woman can determine the sex of her child by eating spicy foods to produce a male or cool foods to produce a female.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
Why do some traits occur together in offspring?

Milestone Explanation:
Some genes are located on the same chromosome (linkage).

---

linkage

Evidence A:
The host of a popular talk-show about sports says that the best baseball pitchers have brown eyes.

---

linkage

Evidence B:
Many microscopic studies show that chromosome pairs can exchange material during meiosis, resulting in a new combination of alleles in that pair of chromosomes. This phenomenon is genetic recombination, which results from crossing over.

---

linkage

Evidence C:
Three scientists demonstrated that purple flowers and long pollen were inherited together in the sweet pea more often (more than 75% of the time) than predicted by Mendel's law of independent assortment (50%).

---

linkage

Evidence D:
A study of human pedigrees shows that certain traits such as hemophilia and color blindness occur at a much higher frequency in males than in females. These traits appear to depend on the inheritance of mutations located on the X chromosome. When a man has both of these traits, studies show that there is a greater than 50% chance that any brothers will have both disorders, or neither one.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
What molecular component in chromosomes carries genetic information?

Milestone Explanation:
DNA carries genetic information.

DNA as genetic material

Evidence A:
Three scientists purified DNA from bacteria that grew in smooth colonies. They put this DNA into bacteria that normally grew in rough colonies. The bacteria that had been given the DNA produced many generations of offspring that formed smooth colonies. This experiment produced the same results when repeated.

Other scientists (many years later) transferred a specific fragment of DNA from bacteria to a plant, and a bacterial trait appeared in the plant.

DNA as genetic material

Evidence B:
Two scientists studied viruses to determine how they infect bacteria. They labeled the DNA and the protein components of the viruses using radioactive chemicals. This allowed them to trace the movement of the DNA and protein. Only labeled DNA entered the bacterial cells during the infection process. Other investigations repeated these studies.

DNA as genetic material

Evidence C:
Scientists have extracted DNA from many different cell types in one organism and from the cells of many different species.

DNA as genetic material

Evidence D:
Scientist Francis Crick and a student named James Watson agreed that DNA might be the genetic material.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
How is the genetic information used to make proteins encoded?

Milestone Explanation:
In DNA, a triplet of nucleotide bases encodes each amino acid in the resultant protein.

---

genetic code

Evidence A:
To determine how the genetic code might work, scientists noted that DNA has four different bases that can be arranged in various sequences. The code must be able to specify the 20 different amino acids found in proteins. Mathematical principles predict the following about the genetic code:

one-base code	specifies	4 amino acids at most
two-base code	specifies	16 amino acids at most
three-base code	specifies	64 amino acids at most
four-base code	specifies	256 amino acids at most

---

genetic code

Evidence B:
Investigators found that removal of three nucleotides from a gene causes the resulting protein to lose one amino acid. However, removal of one or two nucleotides from a gene causes much more disruption in the resulting protein structure. Other scientists quickly repeated these experiments and got the same results.

---

genetic code

Evidence C:
Many types of chemical analysis have shown that DNA contains about equal amounts of four different components (the nucleotides, which contain bases abbreviated A, G, C, and T). In contrast, proteins are made of 20 different components (amino acids), and they vary in amount in different proteins.

---

genetic code

Evidence D:
A shampoo is advertised as containing DNA and able to enrich hair.

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Copymaster 1-3: Evidence Cards

MILESTONES IN UNDERSTANDING GENETICS

Question:
How does a new, heritable trait appear in a population?

Milestone Explanation:
Mutations change the structure of DNA in reproductive cells (gametes).

---

mutations

Evidence A:
People who build large muscles through exercise will have children who also have large muscles.

---

mutations

Evidence B:
A scientist named Hermann J. Muller exposed fruit flies to increasing doses of radiation in the form of X rays. He kept careful records of the number of mutant traits that appeared in their offspring. Muller found that there was a direct correlation between the number of mutations and the amount of radiation: more X rays produced more mutant offspring. (Later research showed that X rays damage chromosomes.) Other scientists have repeated this experiment, and similar experiments have been repeated many times.

---

mutations

Evidence C:
Investigators found that removal of three nucleotides from a gene causes the resulting protein to lose one amino acid. However, removal of one or two nucleotides from a gene causes much more disruption in the resulting protein structure. Other scientists quickly repeated these experiments and got the same results.

---

mutations

Evidence D:
Investigators at the Toronto Hospital for Sick Children studied the DNA of children who have cystic fibrosis (CF). The investigators also studied the parents of these children. They found that these children and their parents have changes in their DNA that are not present in unaffected children or in persons who do not carry the CF gene. Further investigation has revealed more than 600 different DNA mutations in the CF gene.

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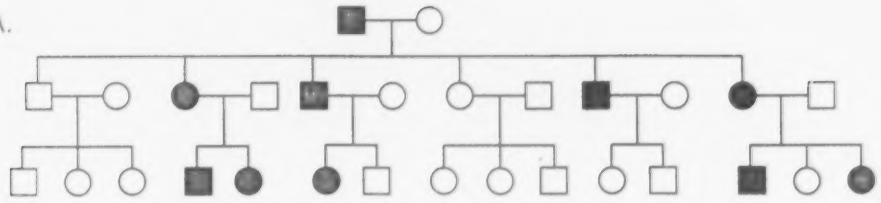
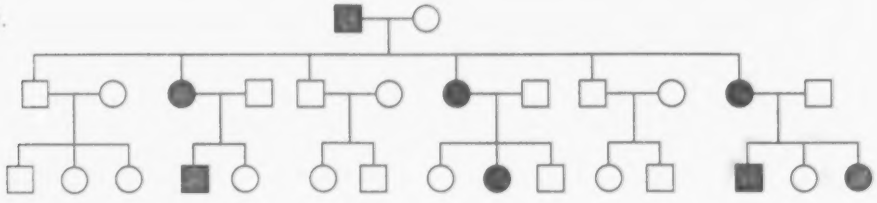
Copymaster 2-1: Pedigrees A-H

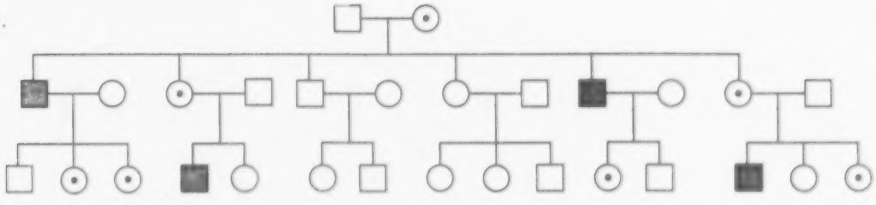
A.



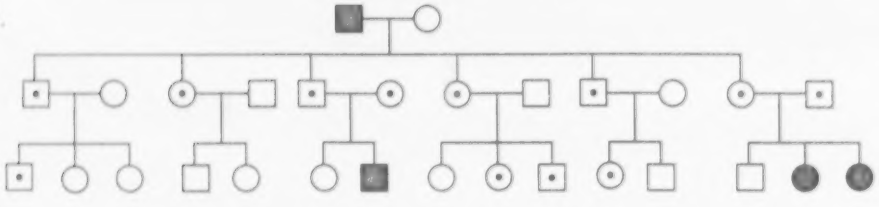
B.



C.



D.



Legend:

□ = male	○ = female
■ = male with trait	● = female with trait
⊡ = male carrier	⊙ = female carrier

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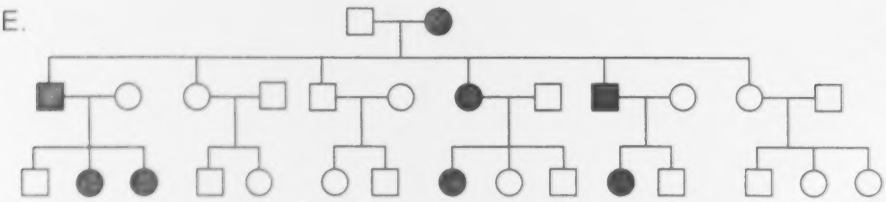
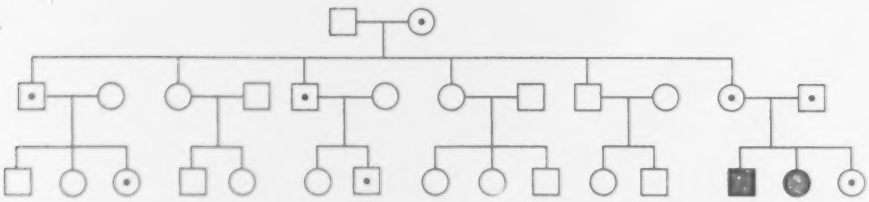
Copymaster 2-1: Pedigrees A-H

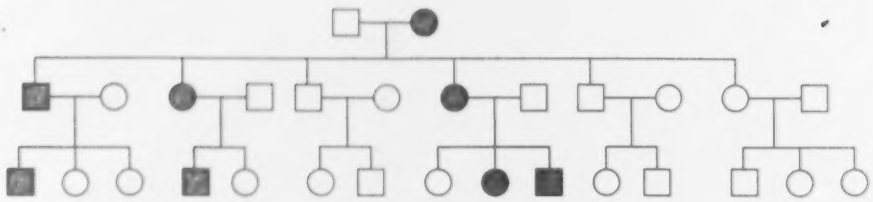
E.



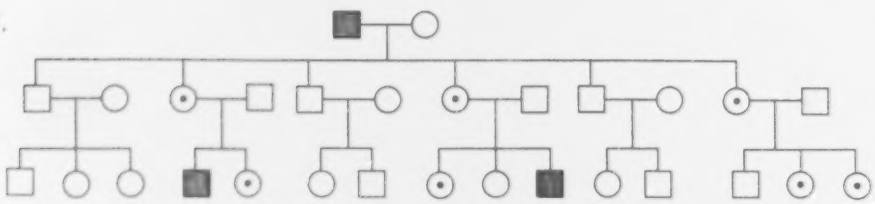
F.



G.



H.



Legend:

□ = male ○ = female

■ = male with trait ● = female with trait

⊡ = male carrier ⊙ = female carrier

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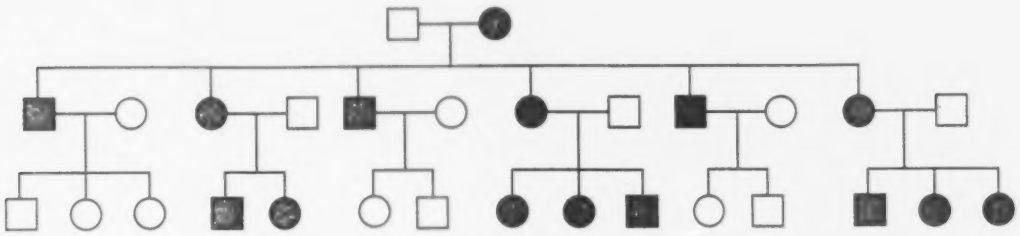
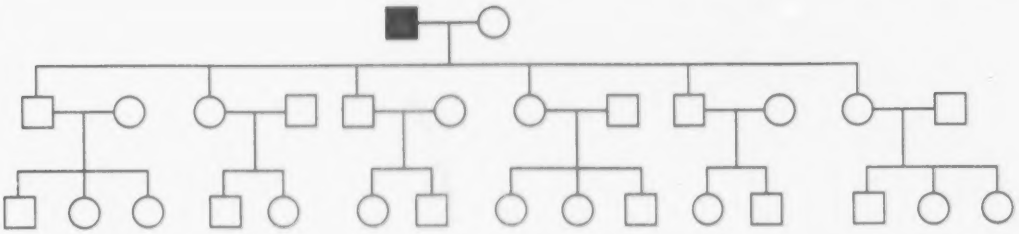
Copymaster 2-2: Pedigrees I and J

I.



J.



Legend: □ = male ○ = female

■ = male with trait ● = female with trait

Note: Pedigrees I and J both show the **same** trait.

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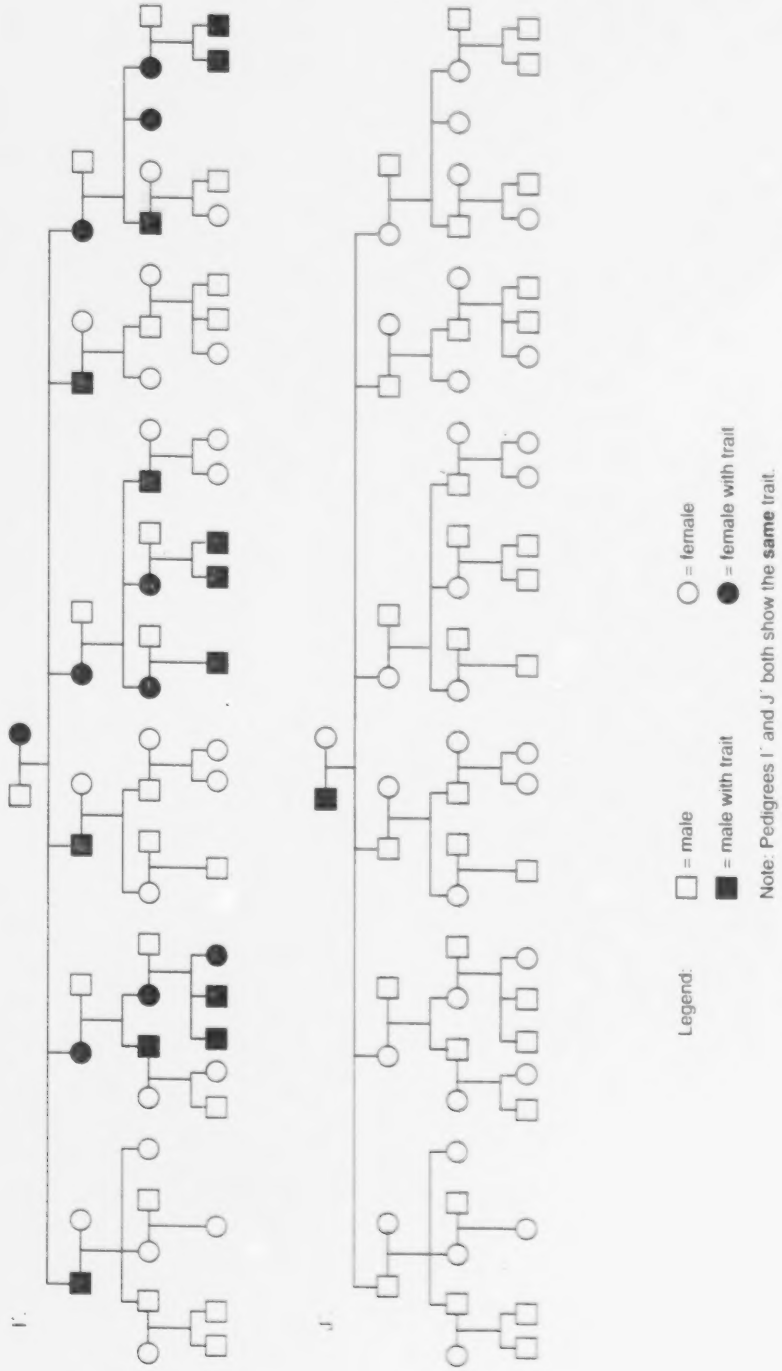
Copymaster 2-3: Pedigrees I′ and J′



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Copymaster 2-4: Building an Explanation

Hypothesis 1:	
Supporting Evidence:	Conflicting Evidence:
Conclusions:	
Hypothesis 2:	
Supporting Evidence:	Conflicting Evidence:
Conclusions:	

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Copymaster 2-5 Science Articles

"Extra" DNA?

How much DNA is enough? Humans have 46 DNA-containing chromosomes in each diploid-cell nucleus; the peas that Mendel studied have only 14 chromosomes. In contrast, a bacterium, which is a prokaryote, contains one large molecule of DNA that serves as its chromosome. (To compare eukaryotic and prokaryotic cells, see the illustration.) Each species has a specific amount of DNA in its chromosome set, but this DNA is not the whole story. Many cells contain "extra" DNA in addition to the major genome. Of course, this DNA is "extra" only in the way people may view it. For instance, students of genetics usually begin by studying the genes found on chromosomes in the nucleus of a eukaryotic cell. In this article, we describe the existence of DNA in addition to the chromosome set.

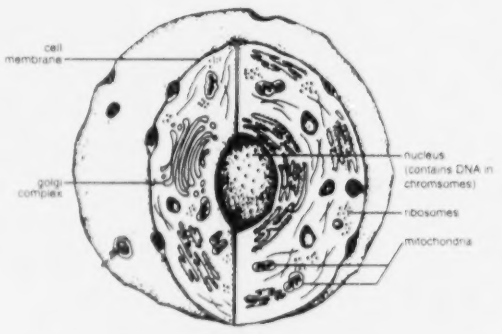
In some bacterial cells, DNA outside the genome occurs as tiny circular molecules known as plasmids. The plasmid DNA replicates on its own, and it has been used by scientists as a tool for cloning.

In eukaryotic cells, some DNA is found outside the nucleus. For example, green plant cells that carry out photosynthesis have small organelles called chloroplasts. Chloroplasts contain the green pigment needed for photosynthesis. In addition, chloroplasts have their own DNA, separate from the chromosomes found in the cell nucleus.

All species of eukaryotes have other organelles known as mitochondria, which also have their own DNA (mtDNA). Mitochondria help generate energy for the cell. A human muscle cell, for instance, may contain several hundred mitochondria in its cytoplasm. Mitochondria help provide energy for the muscle to contract. The mtDNA in each of these mitochondria can replicate on its own, separate from the DNA of chromosomes in the nucleus.

Human mitochondrial DNA has been fairly well studied. Each mitochondrion has multiple copies of its mtDNA, and each copy is made up of 16,569 base pairs arranged as a double-stranded, circular molecule. The entire mtDNA sequence was identified in the 1980s. It includes genes that code for transfer RNAs, ribosomal RNAs (different from those in the rest of the cell), and a few enzymes needed for the energy-related functions of the mitochondria. MtDNA has a higher rate of mutation than does nuclear DNA, and molecular biologists have identified some disorders in humans that result from mutant mitochondrial genes. As you might expect, given the role of mitochondria, these disorders often involve defects in energy production. Others involve problems related to muscles and nerves.

Prokaryotic Cell



Eukaryotic Cell

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Copymaster 2-5 Science Articles

Sperm Meets Ovum

What happens when sperm (male gametes) contact the ovum (female gamete)? Although many sperm reach the ovum, only a single sperm enters and fertilizes the female gamete. What enables the sperm to reach this destination? Sperm are propelled by a whiplike motion of the sperm tail. Once in the vicinity of the ovum, sperm move specifically toward it.

To reach the ovum, sperm have to pass through the uterus and into the fallopian tubes, where fertilization occurs. This path is an enormous distance compared with the tiny size of the sperm, and the sperm require much energy during this journey. Sperm rely on energy release in the mitochondria to power their movement. Mitochondria are found in the upper tail section of sperm.

Sperm are tiny compared to the ovum, which is a very large cell. The ovum's cytoplasm contains chromosomes that have partially completed meiosis, structures that help process new proteins, and many mitochondria.

Once a sperm successfully enters and fertilizes the ovum, it no longer needs its long tail. The tail section disintegrates after the sperm penetrates the ovum, and only the sperm nucleus, which carries the paternal chromosomes, survives inside the ovum. Other dramatic changes take place in the membrane of the ovum that prevent the entry of any additional sperm. Changes induced by the entry of the single sperm include the formation of a protective layer around the newly fertilized ovum. In addition, entry of the sperm stimulates completion of meiosis in the ovum in preparation for the final combination of paternal and maternal chromosomes in the nucleus of the new zygote.

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Copymaster 3-1: HD Clues Presenting Familial Relationships and Health Data

HD Clues for Team 1

1

Horace had only one child, a son named Allen, who was born in 1916.

1

Martha married Horace in 1910, when she was 24 years old. Horace was 29 at the time.

1

Martha's granddaughter, Kristen, was the twin who never married, but her identical twin sister, Ann, did marry.

1

Ann's father, Allen, died of Huntington disease at the age of 60, 10 years after symptoms appeared.

HD Clues for Team 2

2

Ann's paternal grandmother, Martha, began to show signs of confused thought at the age of 55.

2

Horace's only son was married to Linda.

2

The twins' older brother, Andrew, looked a lot like his mother, Linda.

2

Kristen was not as close emotionally to her identical twin sister, Ann, after Ann married Greg in 1961. Ann was 17 and Greg was 19. Kristen never married.

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Copymaster 3-1: HD Clues Presenting Familial Relationships and Health Data

HD Clues for Team 3

3

Martha died in 1951 at the age of 65, of what might have been Huntington disease. She died before her youngest grandchild, Debbie, was born.

3

When Bill married Andrew's youngest sister, Debbie, in 1974, she was 19 and he was 22. Bill had no idea he was marrying into a family with a history of HD. He knew of no one in his family who had the disease.

3

Debbie and her husband, Bill, bought a savings bond for their granddaughter, Cathy. Cathy's mother, Paula, thanked her parents for this gift.

3

Andrew was one year older than his twin sisters, but he was 12 years older than his sister Debbie.

HD Clues for Team 4

4

Horace was born in 1881 and died at the age of 72. He was very active and had a clear mind throughout his life.

4

Ann and Greg realized when their son, Nathaniel, was born in 1962 that Ann's father had Huntington disease. Ann may have inherited it too. Ann and Greg were so poor and so worried about Ann's health that they placed their son, Nathaniel, for adoption by the Wu family.

4

Jean's husband, Nathaniel, wanted her to name their son after him, but she insisted on the name "Peter" instead. The year was 1992. Jean was 32 years old.

4

Debbie was only 7 years old when her older sister, Ann, and her husband, Greg, placed their son for adoption.

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Copymaster 3-1: HD Clues Presenting Familial Relationships and Health Data

HD Clues for Team 5

5

When Christina was a little girl, her father, Andrew, began to show symptoms of HD. His movements became awkward and his muscles twitched. Andrew was 37 years old.

5

Martha's grandson, Andrew, died of HD when he was 50 years old, 13 years after his symptoms first appeared. The year was 1993.

5

Allen's grandson, Joseph, was born in 1970. Joseph was three years younger than his sister, Christina, and five years older than his cousin, Paula.

5

Joseph feared Huntington disease. His big sister, Christina, began to show symptoms when she was only 26 years old. Joseph passed his 27th birthday, however, without showing symptoms of the disease.

HD Clues for Team 6

6

Evan's Aunt Kristen got sick soon after his Aunt Ann. At the time she showed symptoms of HD, Ann was 39 years old. Kristen was 40 when her HD symptoms appeared. Evan's mother, Debbie, was healthy.

6

When she was a teenager, Paula liked to "give orders" to her younger brother, Evan, who was born in 1982. She was seven years older than Evan.

6

When Paula gave birth to Cathy in 1997, Paula's mother, Debbie, became a grandmother. She did not feel like a grandmother; she was only 42 years old, and kept active physically and mentally, attending dance class and running her own business.

6

Evan is younger than his cousins, Joseph, Christina, and Nathaniel. Evan is 8 years younger than his brother-in-law, Bob, and only 10 years older than Nathaniel's son, Peter.

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Copymaster 3-1: HD Clues Presenting Familial Relationships and Health Data

HD Clues for Team 7

7

Jama gave birth to a daughter, Christina, in 1967. Jama was 22 years old.

7

Paula and her brother, Evan, are healthy. Their cousin, Christina, is not as lucky; she has suffered from twitchy muscles and other symptoms of HD since 1993, when she was 26 years old.

7

Jama married Andrew in 1965, when she was 20, long before she knew that Andrew had inherited the fatal disorder known as Huntington disease.

7

Bob and his father-in-law, Bill, took photos the day Bob's daughter, Cathy, took her first steps. Bob's wife, Paula, was away, visiting her brother, Evan.

HD Clues for Team 8

8

Paula's mother, Debbie, has not shown any symptoms of HD as of the age of 42, although Debbie's twin sisters began to show symptoms before this age.

8

When Nathaniel was 33 years old, in 1995, he began to suffer from lapses of memory. His mother, Ann, and her twin sister still appeared healthy when they were 33. Later, they developed HD.

8

Linda was alert and active in sports throughout her fifties. By the time she reached 70, in 1992, she no longer played tennis, but she was still healthy.

8

Nathaniel's mother, her twin sister, and Nathaniel's Uncle Andrew all showed symptoms of HD when they were fairly young. Nathaniel's mother was 39, his Aunt Kristen was 40, and his Uncle Andrew was 37 when they showed HD symptoms.

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Copymaster 3-2: HD Clues Presenting Molecular Data (one copy per team)

In 1993, researchers developed a test for the mutant HD gene. A particular trinucleotide may be repeated many times in the mutant gene. The following clues provide molecular data about the family you have been studying.

HD Pedigree - Molecular Data

By the time Bob married Paula, he knew that the genetic data for her trinucleotide repeat count were (13, 12). He wasn't tested because his family had no history of HD.

When Evan heard the results of the genetic tests done on his parents and sister, he chose not to be tested.

Christina was tested for HD the year her father died of the disease. Her trinucleotide repeats counts were (93, 7).

Joseph had a genetic test for HD before he would ask Becky to marry him. When he found out his test results were (7, 6), he asked her right away. The year was 1993; Becky was 24 years old.

Although Becky's family had no history of HD, she offered to be tested because she knew how concerned her husband, Joseph, was about this disease. Her counts were (20, 8).

Andrew's wife, Jama, had these counts for trinucleotides in the gene associated with HD: (7, 18).

In 1992, at age 30, Nathaniel Wu applied for a job as a laboratory scientist. As part of the application process, he was tested for several genetic disorders and was shocked to find out that he had inherited an HD mutation. His trinucleotide repeat counts are (72, 19).

Dr. Engle had been so curious about the possibility of genetic anticipation in Allen's family that he preserved a tissue sample from Allen and his wife, Linda, in 1957. Forty years later, an HD researcher tested the samples and found these results: Allen (46, 13); Linda (6, 22).

In 1993, the year Andrew died of Huntington disease, the diagnosis was confirmed by a genetic test that showed he had one mutant HD gene with 69 trinucleotide repeats. The homologous copy had only 6 repeats, apparently inherited from his mother.

The twins, Kristen and Ann, were tested for HD. Here are the results: Kristen (64, 22); Ann (64, 22).

Greg's counts were (11, 19).

Nathaniel knew his son, Peter, had a 50 percent chance of inheriting HD. The chance could have been higher, except that his wife's counts for trinucleotide repeats in this gene were only (8, 19).

Debbie was terrified that she had inherited HD, as had her three elder siblings. When she was tested, she found out that her trinucleotide counts were (13, 6).

Bill's counts were (8, 12).

We have no record of the trinucleotide repeat counts for Horace or Martha; they lived too long ago to be tested.

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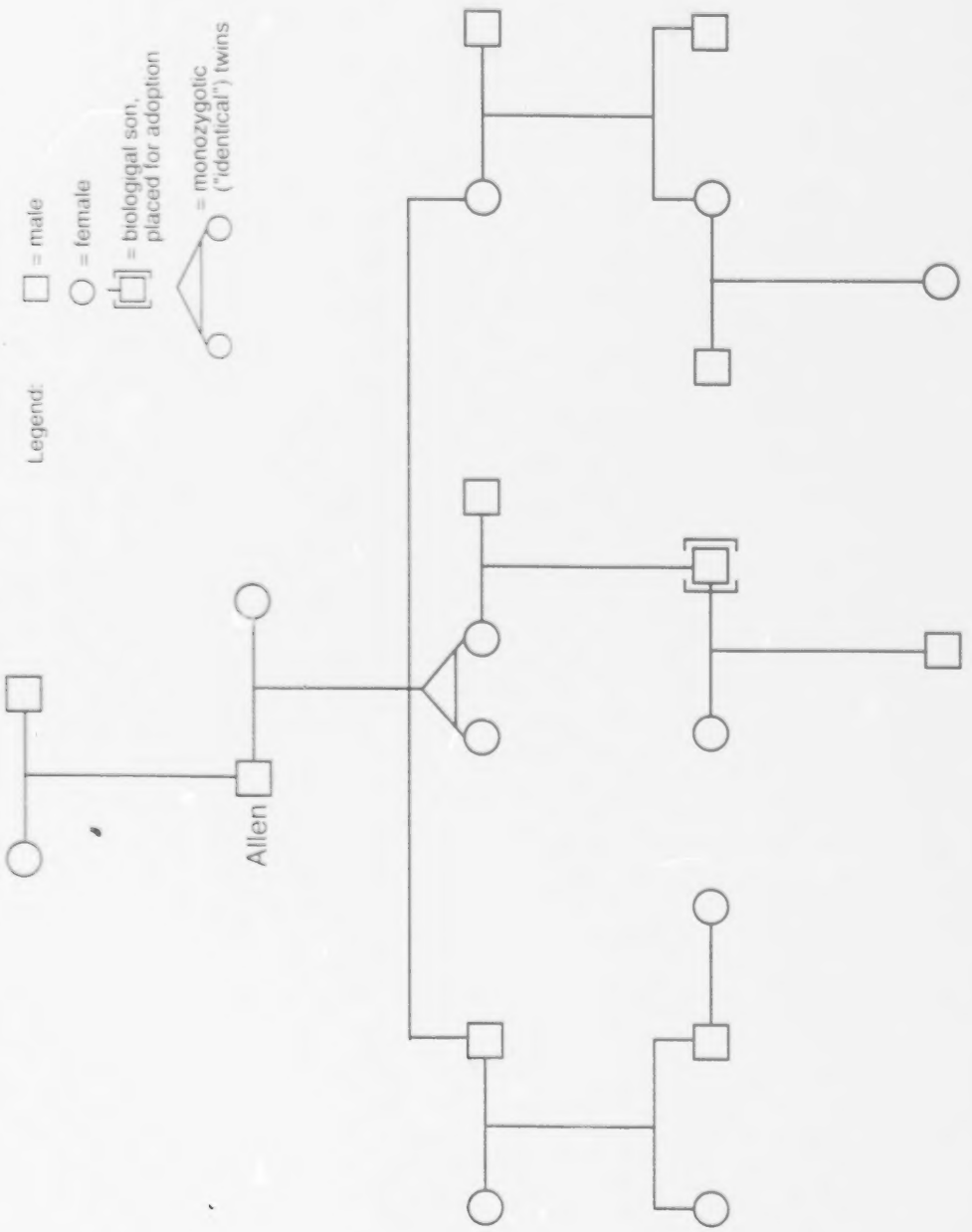
Copymaster 3-3: Template for the HD Pedigree



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Copymaster 3-4: Science Article About a Genetics Discovery

New Genetics Discovery: Trinucleotide Repeat Expansion

Although most DNA sequences are transmitted from parent to child as exact copies, there are occasional exceptions. There can be an increase or decrease, for example, in the number of copies of a repeated trinucleotide sequence found in certain genes. The change occurs when the gene is passed from parent to offspring. Instability of the trinucleotide repeats increases if the gene has a critical number of copies of the trinucleotide repeats in a row. This phenomenon is called ***trinucleotide repeat expansion***, and it plays a role in the inheritance of several genetic disorders in humans.

Two of these disorders, myotonic dystrophy (DM) and Huntington disease (HD), are inherited as autosomal dominant traits, but the features of the diseases can vary widely from one person to another, and from one generation to another. The mutant genes for both DM and HD have been identified. The mutant HD gene is located on chromosome 4, and the mutation that causes DM is on chromosome 19.

Both mutant genes contain a region of DNA where three specific nucleotides of DNA are repeated over and over—many times more than the number found in normal copies of these genes. The number of copies of the trinucleotide repeat influences symptoms in the associated disorder.

Genetic tests can determine the number of repeats in each copy of the DM- or HD-associated gene. (An individual inherits one copy of a gene from the mother and one from the father.) The higher the number of repeats, the earlier the symptoms appear, and the symptoms may be more severe, particularly with DM. For example, DM patients with about 50-80 copies of the trinucleotide CTG have mild symptoms such as cataracts late in adulthood. Other DM patients have more severe symptoms, such as muscle wasting and retardation as young adults. These patients generally have 80 to a few hundred copies of CTG in the mutant gene. The most severely affected patients show characteristic muscle problems and retardation when they are children. Individuals with severe DM have hundreds to more than 2,000 copies of the CTG trinucleotide repeat.

People who have HD can have anywhere from about 39 copies of the sequence CAG to more than 120 copies. Two-thirds of HD patients have 40-50 copies of the CAG trinucleotide in the HD mutant gene. A copy of the nucleotides in the gene associated with HD is passed from parent to child without change, except for those nucleotides represented by the letters in bold in the illustration. The number of times CAG is repeated can change during transmission, either expanding or contracting. As a result of this change, the child who inherits the mutant HD gene could exhibit a different phenotype from that of his or her parent, perhaps with a different age of onset. The chance that the number of repeats will expand is greater if the mutant HD gene is inherited from the father than it is from the mother.

References

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DNA sequence from a mutant gene for HD, with the CAG repeat in the middle:

AGCTAGCAGACTGATCGATGTACGTACGTTAGCTAGTGCATGAGCGATGCTAGCTTAGCTAGT
CTATGCATTAGCAT**CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGC**
CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG
CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCA
GCAGCAGCAGCAGCAGTGGCATCGATGCATGATCTAGCATAGGACTCTAGAGACCCCATGCA
TTACGATTACGATTATCGACCCCATAGGGATCGTACGATGCATCGATGCAGCATG

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Copymaster 3-5 Part A:
DM Clues Presenting Familial Relationships and Health Data

Sean gets a lot of attention from his grandparents, Kevin and Elizabeth, because he is their only grandchild. Elizabeth was 55 when Sean was born. Kevin was 54 and ill.

Sean spent weeks at birth in 1991 in intensive care because his severe weakness made breathing difficult. Doctors suspected he had a severe form of myotonic dystrophy. His parents, Maureen and Jonathan, were very worried.

Amelda and Bob had three children. Their oldest son, Kevin, and youngest son, David, were 6 years apart. A middle child, Miriam, was born in 1938, 1 year after Kevin. She had cataracts when she was 36 and suffered from muscle weakness.

When Kevin was 36, in 1973, he began to go bald and his eyesight weakened. The doctor discovered he had cataracts, which are unusual in an adult that young. Kevin also had moderate muscle weakness. His only daughter, Maureen, was 9 years old at that time.

Kevin's mother, Amelda, had cataracts by the time she reached age 45 in 1967. His father, Bob, was healthy all his life and died at age 80, in 1994, the same year Kevin died.

Amelda suffered from mild muscle weakness, but she lived to be 71 years old, dying in 1993, when her oldest son, Kevin, was 56 years old.

Amelda's mother, Bertha, developed cataracts in her late 50s, but otherwise she had no serious health problems until she had a heart attack at age 72. She died in 1965, at age 73.

When Bob married Amelda in 1940, he was 26 years old, and she was 18. They had 3 children and were happy together for 53 years, until Amelda died. Bob died a year later.

Wilbur was strong and active, but he died in a train crash in 1942 at age 52. His widow, Bertha, was devastated, as was his only child, Amelda.

Kevin's daughter, Maureen, married Jonathan in 1985, when she was 21 years old. Six years later their son, Sean, was born.

In 1997, at the age of 47, Jonathan is very athletic, with strong muscles, good coordination, and sharp eyesight. His wife, Maureen, was less fortunate. She had several miscarriages before her son, Sean, was born.

A few years after her marriage at age 25, Maureen got cataracts. A year later doctors discovered she had a heart-rhythm problem and muscle weakness. She died young, at age 33, when her son Sean was only 6 years old.

David married Julie in 1965. She was 20 years old, 2 years younger than David. As of 1997, both are healthy and happy.

David and Julie had two daughters: Cindy (born in 1965) and Jean (born in 1968). Both daughters are healthy and active in sports.

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Copymaster 3-5 Part B: DM Clues Presenting Molecular Data

A genetic test can show the number of trinucleotide repeats in the gene whose mutant form causes DM. The results for Sean's parents were Jonathan (10, 15); Maureen (621, 12).

The year Amelda died, she was tested to determine the number of trinucleotide repeats in her mutant DM gene. The results were (211, 6). Her husband, Bob, was also tested. His results were (6, 10).

The year Kevin's mother died, Kevin and his wife, Elizabeth, had genetic testing done. The results showed the number of trinucleotide repeats in the gene associated with DM. For Elizabeth, the numbers were (12, 14); for Kevin, they were (400, 6).

Although Sean was a baby, his severe symptoms and the health problems of his mother alerted doctors to test him for DM. He had a remarkably high number of trinucleotide repeats in one copy of the gene. His test results were (1232, 15).

David was tested for DM. His trinucleotide repeat numbers were (6, 10). His wife, Julie, was tested, too. Her results were (18, 19).

Cindy's test results were (6, 19) for trinucleotide repeats in the gene associated with DM. Her sister's results were (10, 18).

Miriam was tested for the mutant DM gene. Her trinucleotide repeats were (430, 10).

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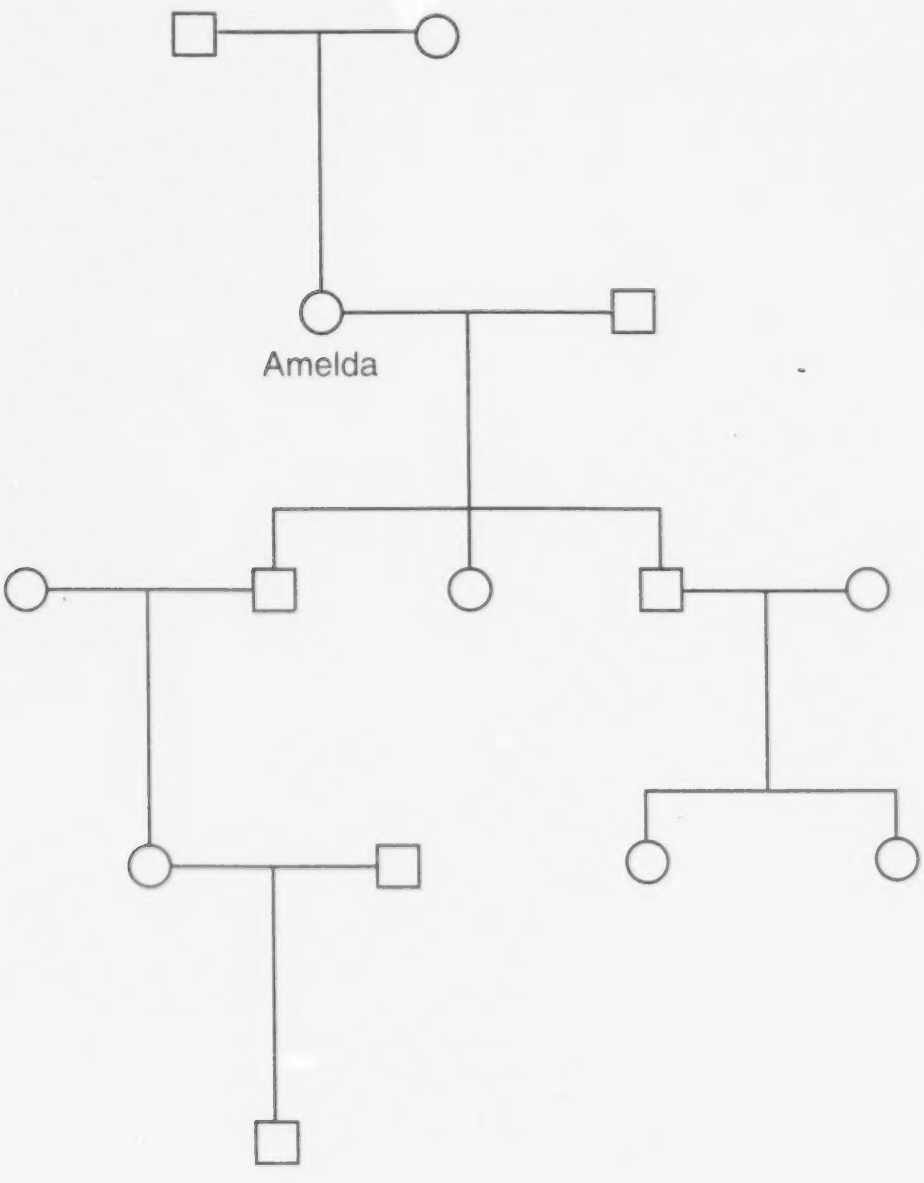
Copymaster 3-6: Template for the DM Pedigree



Legend: □ = male ○ = female

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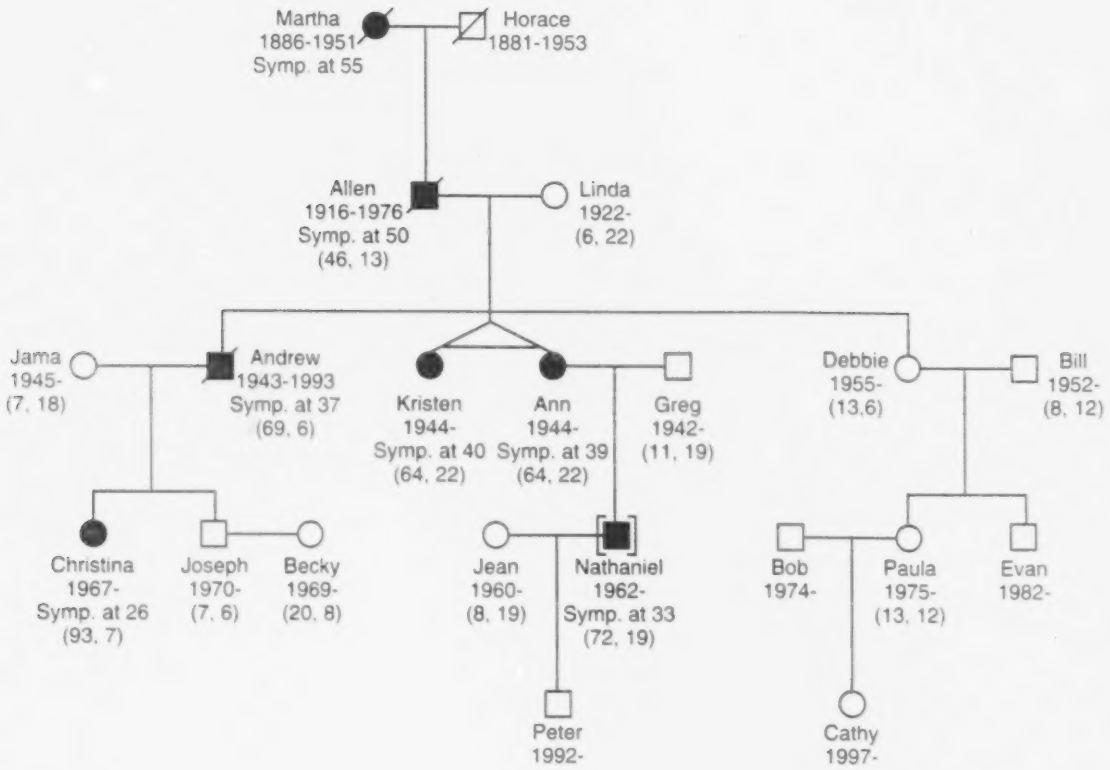
Copymaster 3-7: Completed HD Pedigree



Legend:

- = unaffected male
- = affected male
- = deceased male
- = biological son, placed for adoption
- = unaffected female
- = affected female
- = deceased female
- = monozygotic ("identical") twins

Symp. = age of onset of HD symptoms

Numbers in parentheses are the trinucleotide repeat counts for the gene associated with HD

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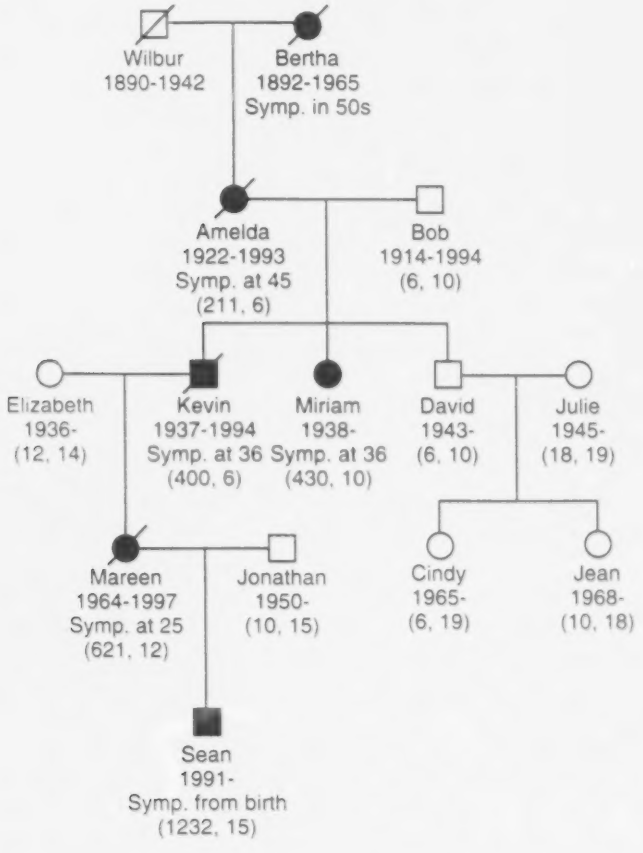
Copymaster 3-7: Completed DM Pedigree



Legend:

- □ = unaffected male
- ○ = unaffected female
- ■ = affected male
- ● = affected female
- ⊠ = deceased male
- ⊘ = deceased female

Symp. = age of onset of DM symptoms

Numbers in parentheses are the trinucleotide repeat counts for the gene associated with DM

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Copymaster 3-8: History of Huntington Disease - Vignettes

Vignette One: The year is 1914

Jeffrey, an enthusiastic young medical student, sits down at the cafe table already occupied by his two friends, Joe and Morris. Jeffrey excitedly shows them a translation of a medical report originally published by a Norwegian doctor, Johan Lund, in 1860. He tells Morris and Joe that one of his professors brought the article to class. Joe reads it quickly and hands it to Morris.

"This is a report of the same genetic disorder described by Dr. Huntington in 1872. But Dr. Lund called the condition 'twitches' instead of 'hereditary chorea,'" Jeffrey points out.

"No, Lund just says that 'twitches' is the common name," Morris replies. "He calls it 'chorea of St. Vitus.'"

"The name isn't the issue," Joe comments. "Both reports are based on multiple case histories and several generations. Huntington mentions a slightly earlier age of onset than does Lund. They both mention the combination of neurological symptoms, including uncontrolled muscle movements, memory loss, and even dementia. And both doctors report the hereditary nature of the disease."

"But neither doctor offers any explanation for the variation in progress of the disease—rapid decline in most patients, but later and slower decline in others. And neither doctor can explain the mechanism that causes the awful symptoms," Jeffrey notes.

"And no one has any idea of a cure..." says Morris. The three young men finish their coffee in silence.

Vignette Two: The year is 1957

Allen and Linda enter the house in silence. Both are thinking about what the neurologist, Dr. Engle, had told them after he examined Allen. The doctor suspected that Allen had inherited a frightening illness he called Huntington's chorea. They had just heard the name of this disorder on the news. The famous folk singer, Woody Guthrie, had this illness. And now, perhaps, Allen had it, too.

Dr. Engle's tentative diagnosis was based in part on the memory losses Allen had been experiencing. At his relatively young age of 40, Allen should not have these lapses. In addition, Linda had mentioned to the doctor that Allen sometimes moved oddly, in an awkward "twitchy" way. When Dr. Engle asked about Allen's parents, he learned that Allen's mother had shown similar symptoms, but they had not even started until she was 55, some 15 years older than Allen is now. She had lived another ten years after the symptoms appeared. Dr. Engle thought that Allen had inherited Huntington's chorea from his mother. That would fit with its pattern of autosomal dominant inheritance. And it would fit with the pattern of genetic anticipation that Dr. Engle had read about in cases of Huntington's chorea and myotonic dystrophy. However, he knew that his colleague, Dr. Randall, was skeptical that genetic anticipation really occurred. It could just be a misperception because of a lack of scientific rigor in the way data were collected as case histories.

However, this scientific debate was far from the reality of life for Allen and Linda. They thought only about Allen's symptoms and the danger that might be ahead for Allen and their four young children. Had they unwittingly passed on this terrible legacy to them?

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Copymaster 3-8: History of Huntington Disease - Vignettes

Vignette Three: The year is 1986

Ann and Greg visit a genetic counselor. Ann has begun to show symptoms of Huntington disease, a disorder that runs in her family. Her brother Andrew is very ill with it, and her father died of the disease. Ann wants to know if she should try to have an adoption agency contact her biological son, Nathaniel, who was placed for adoption when he was a newborn. Should she warn him that he is at risk? Now that Ann knows that she has the disorder, the known risk for Nathaniel is 50 percent. He is 24 years old, an adult who might want to be tested. The counselor explains to Ann that, although the gene for HD had just been mapped to chromosome 4, there is still no widely available test, although one might be available soon. She suggests that Ann should wait until that time to tell Nathaniel of his biological family and the risk of HD.

Vignette Four: The year is 1997

Jean Wu makes an appointment with a genetic counselor. She had been to this office several times because her husband, Nathaniel, has Huntington disease in its early stages. This time, however, she has come to talk to Dr. Feynmann about her son, Peter. She wants to have her son tested for the disease. She worries constantly about not knowing her son's fate with regard to HD. Dr. Feynmann explains that, although Jean and her husband have been tested, the current policy of the clinic (and most clinics) is to withhold testing for children who are minors and who do not show any symptoms. That way the minors can make the choice to be tested for themselves when they are adults, rather than having a parent decide for them.

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Copymaster 4-1 *Worksheet for a Discussion About Policy*

Current policy: To withhold genetic testing for Huntington disease for asymptomatic minors	
Reasons to maintain policy	Reasons to change policy

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Student Pages for Classroom Activities

Photocopy these pages for student use.

Engage Activity
Scientific Investigation

Procedure

1. Share materials with your team, but work individually. Select a peanut and carefully observe it to determine the distinguishing characteristics that identify this particular peanut. Record your observations on a piece of paper. *Do not mark or crack the peanut.* You may use the equipment provided to help you with your observations.
2. Return each team member's peanut to the bowl. Mix up the peanuts.
3. Use your notes to find your peanut again.
4. Raise your hand if you are *absolutely certain* you have found your own peanut.
5. What evidence did you use to locate your peanut and distinguish it from the others in the bowl?
6. Exchange your team's bowl of peanuts and observation notes with those from another team. Now work individually with one set of observations from another student and try to find the particular peanut it describes.
7. Raise your hand if you are *absolutely certain* that you have found the correct peanut.

Analysis

1. What observations were most valuable in finding a specific peanut?
2. What role did your notes or the notes of another student play in helping you to locate a particular peanut? (If your memory was a better guide, what does that say about your notes?)
3. People often confuse *observations* with *inferences*. *Observations* are collected using your senses, either directly or expanded by technology using devices such as microscopes, X-ray machines, or microwave sensors on satellites. *Inferences* are ideas or conclusions based on what you observe or already know. Using this distinction, which of the following statements are observations and which are inferences?
    - If this peanut is roasted, the seeds will not germinate.
    - The shell has a rough surface.
    - The shell is uniformly colored.
    - The peanuts came from a plant.
    - The shell has two lobes and is smaller in diameter between them.
    - This peanut will taste good.
    - Squirrels would eat these peanuts.
    - The surface markings on the shell are in rows, running lengthwise.
4. Now, look at your notes and label any inferences that you included.
5. What counts as evidence in science?
6. What makes science objective? Why is objectivity important?

Activity 1
Standing on the Shoulders of Giants

If you make a scientific discovery, will people still rely on it one hundred years later? Scientists continue to use the theories of inheritance described by Gregor Mendel (Figure 1-1)—they are remarkably durable after more than a century. Since the rediscovery of Mendel's work in about 1900, biologists have made great strides in determining the mechanisms of heredity. Knowledge about genetics has expanded in the last two decades with technical advances in molecular biology and, most recently, with the work of the Human Genome Project (HGP). This huge project will identify genetic relationships (maps) and chromosomal locations of all human genes and will attempt to determine the DNA sequence for the entire genome of *Homo sapiens*. Mapping and sequencing will be done for other species, too, including selected bacteria, yeast, a plant, and several animal species.

Discovery in the HGP or any field of science occurs in stages. Similarly, the history of genetics is much more than a simple record of dates, names, and discoveries; it is an account of how our understanding of inheritance and the gene has grown and changed. Modern geneticists (Figure 1-2) are "standing on the shoulders of giants" who came before them.

Procedure

Part I: Milestones in Understanding Genetics

Much of the information about genetics in your biology textbook would have amazed biologists a hundred years ago. Those scientists, driven by curiosity to answer complex questions of heredity, slowly pieced together layer after layer of the milestone explanations that we now accept as valid. The most significant explanations stand as milestone events, each of which marks a great shift in our understanding. Think about what scientists needed to know *before* they could add each new milestone to the body of genetics knowledge. You are going to build a sequence of milestone explanations. When you do, your sequence may reflect the actual progress of genetics during the last hundred or so years, or it may reflect other ways that history could have played itself out during these early years of discovery.

1. Your team will receive a set of eight milestone explanations of inheritance. Decide how these milestone explanations could form a meaningful sequence, and be prepared to report your sequence and the reasons you chose it.

courtesy of Dr. Vítězslav Orel, Mendelianum, Moravian Museum, Brno, Czech Republic

Figure 1-1 Gregor Mendel (1822-1884), a pioneer in the study of inheritance: His explanations were based on observation of traits, use of careful records, and the mathematical analysis of his data.

2. Your teacher will show you the actual sequence of milestone events that occurred in the history of genetics. Compare it to the sequence you helped build with the class. Might the events have occurred just as easily in the order you built?

3. What technologies or cultural issues might have influenced the timing of the milestones and other discoveries in genetics?

Part II: How Good Is the Explanation?

The milestone explanations you have been using have lasted for many years. Why? Use this part of the activity to explore how we know whether a scientific explanation is on the right track and, thus, whether it will survive the test of time.

4. Your teacher will give your team a set of Evidence Cards and one Milestone Card. Your first task is to evaluate the Evidence Cards and keep only those that are credible. To determine whether the information on any given Evidence Card is credible, discuss with your teammates the criteria you can use to evaluate the evidence. Write your reasons for accepting or rejecting the stated evidence.

5. Now decide whether the evidence you retained is helpful in supporting or refuting the milestone explanation. Explain your decision. *(Hint: Some evidence will be helpful; other evidence may not be related to the milestone explanation.)*

Analysis

Not all scientific discoveries are great milestones that change our understanding of the natural world. Scientists put an enormous amount of work into even relatively simple discoveries, as you would expect when you consider the rigors of investigation. These small pieces provide a valuable part of a larger puzzle. Gradually, we build our understanding of inheritance. The rarity of great leaps in understanding can be a frustrating aspect of scientific work. Science is carried out by people who must earn a living and

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Figure 1-2 Modern studies in genetics: Although modern geneticists use molecular techniques such as cloning and sequencing, geneticists continue to use microscopic techniques, particularly in cytogenetics.

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who want to fulfill personal goals, factors that might influence their work. Think about the social and cultural setting in which research takes place as you respond to these questions.

1. What does science try to do?
2. How do we know an explanation is on the right track?
3. What counts as credible evidence in science?
4. Mendel developed a simple, yet elegant, system to explain inheritance. What has happened to his system?
5. Begin to make a poster that records your ideas about the characteristics of science, if your teacher instructs you to do so.

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Activity 2
Puzzling Pedigrees

How do scientists decide the direction for their research? For example, scientists want to know how genes are involved in cancer. This problem is too large and complex to tackle all at once.

Scientists, therefore, break large problems into smaller, focused parts. They propose a testable explanation, called a hypothesis, to try to answer one of the smaller questions. These hypotheses show where and how to look for answers.

As scientists make observations and record data, they usually find that the new evidence reinforces what they already know. Sometimes, however, the new data do not fit what is known. If the *evidence is reliable*, scientists cannot just ignore it. Instead, they must look for new explanations to extend or modify what is known. In this activity, you will put your skills of observation and your previous knowledge of heredity to work to study some puzzling patterns of inheritance.

Procedure

Part I: Review of Inheritance Patterns

1. Determine the *most likely* pattern of inheritance for each of the pedigrees shown in Figure 2-1 on page 174. To help you, Figure 2-2 lists the characteristics of the four patterns of inheritance that you studied in the genetics unit of your biology class. Your teacher will direct you to work on this task alone or with a partner. You will have 10 minutes to complete this task.

Part II: Puzzling Pedigrees

2. Study two new pedigrees (Pedigrees I and J) shown in Figure 2-3. *Both pedigrees illustrate the same trait.* Try to identify the inheritance pattern illustrated by these two pedigrees. Explain your responses, stating specific examples to support your explanation.

Part III: Testing an Explanation

How good is the explanation of inheritance you suggested in Part II? When you suggested an inheritance pattern, you were making a hypothesis. A scientific hypothesis is a *testable* explanation. To determine how good your hypothesis is, use evidence to test it.

3. Analyze the data (evidence) you have observed from the pedigrees to see whether they support or conflict with your hypothesis. (Your teacher will provide a worksheet for your convenience.) Record your explanation for the inheritance patterns in Pedigrees I and J as "Hypothesis 1." (Remember that both pedigrees demonstrate the *same* trait.) Next, list evidence that *supports* your

Figure 2-1 Pedigrees showing the inheritance of eight human traits

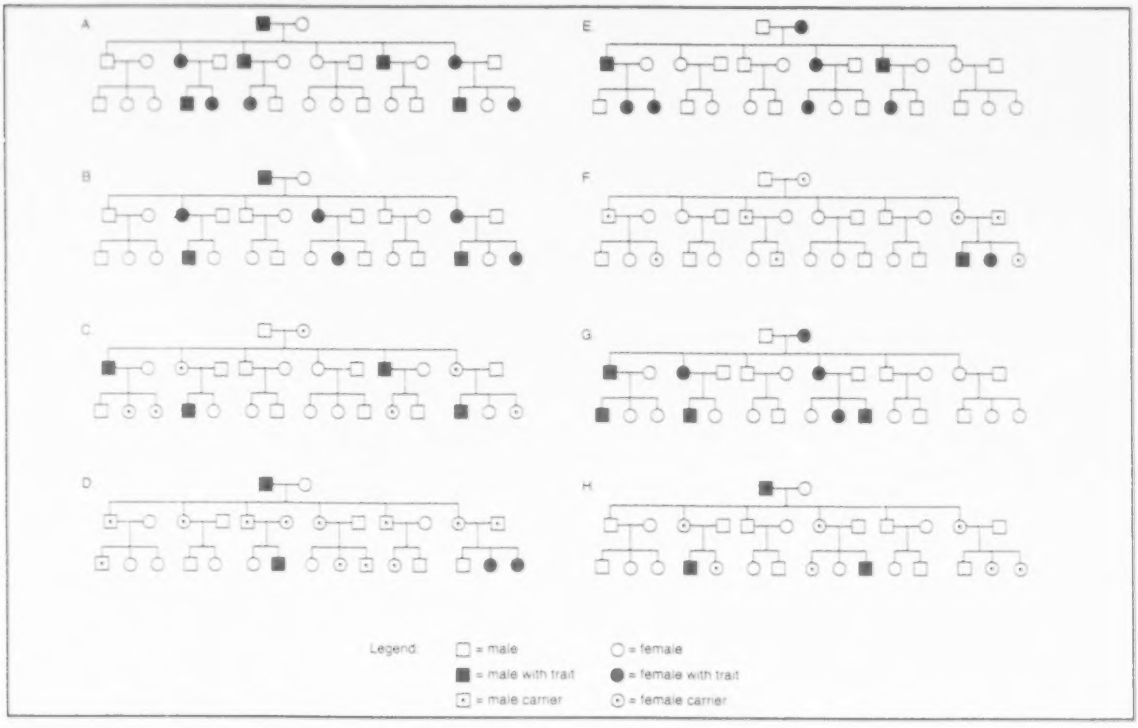

Figure 2-2 Four patterns of inheritance

Autosomal dominant	Autosomal recessive
Males and females are equally likely to have the trait. Traits do not skip generations (generally). The trait is present whenever the corresponding gene is present (generally). There is male-to-male transmission.	Males and females are equally likely to have the trait. Traits often skip generations. Often, both parents of offspring who have the trait are heterozygotes (they carry at least one copy of the allele). Only homozygous individuals have the trait. Traits may appear in siblings without appearing in their parents. If a parent has the trait, those offspring who do not have it are heterozygous carriers of the trait.
X-linked dominant	**X-linked recessive**
All daughters of a male who has the trait will also have the trait. There is no male-to-male transmission. A female who has the trait may or may not pass the gene for that trait to her son or daughter.	The trait is far more common in males than in females. All daughters of a male who has the trait are heterozygous carriers. The son of a female carrier has a 50 percent chance of having the trait. There is no male-to-male transmission. Mothers of males who have the trait are either heterozygous carriers or homozygous and express the trait. Daughters of female carriers have a 50 percent chance of being carriers.

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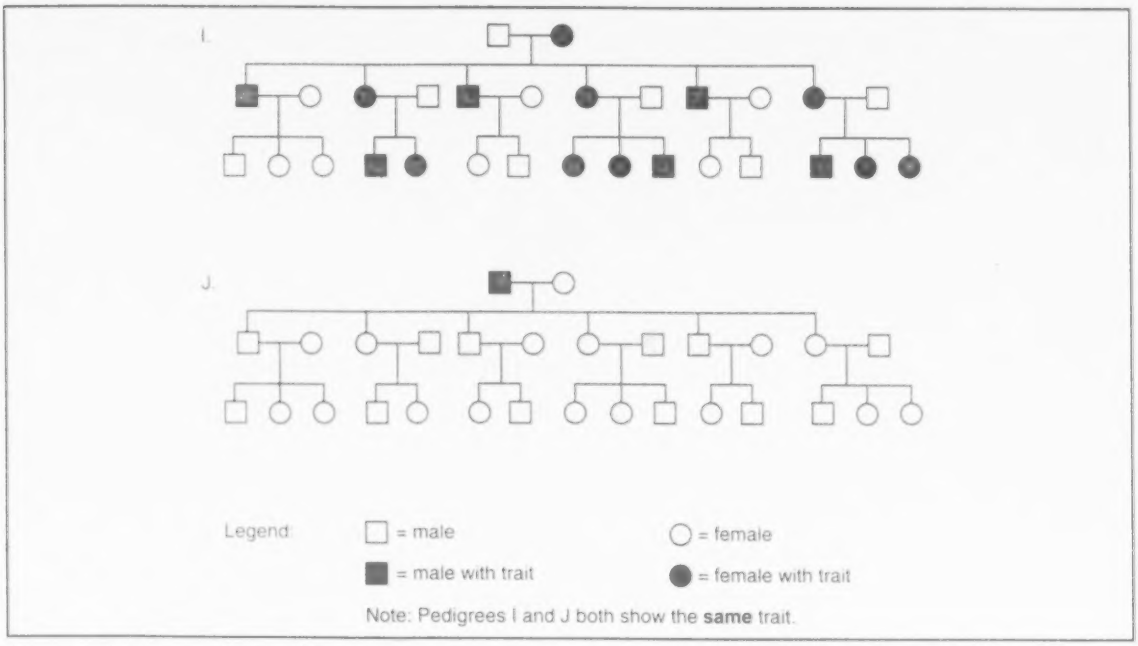

Figure 2-3 Two puzzling pedigrees

explanation and evidence that *conflicts* with it. Refer specifically to Pedigree I or J as you report this evidence.

4. You can reason, calculate, or do experiments to test a hypothesis. For example, assume that the mother in the first generation of Pedigree I is heterozygous. For a hypothesis of "autosomal dominant":

   a. Consider each child singly. What is the probability that the mother will transmit the gene in question? (You can calculate the probability based on what you know about autosomal dominant inheritance.)

   b. You actually can model the events in the pedigree and use the data to test this hypothesis. Use a coin to represent the two alleles involved in this trait. Heads will represent the allele responsible for the trait. Tails will represent the allele that does not produce the trait. Model the inheritance shown in the second generation by tossing the coin six times, once for each child. Record the results, using a chart like the one illustrated in Figure 2-4.

   c. Your coin toss gave you empirical (observable) data. You also can calculate the likelihood that all six children inherited the trait from the female parent. *(Hint: Recall your answer to Question 4a, and remember that the probability for each child is based on a separate event. Use the product rule, based on the second law of probability, to find the probability for all six children.)*

5. Suppose that the mother exhibiting the trait in the first generation of Pedigree I is homozygous for a dominant trait. Would that explanation be consistent with the results you observed in her offspring

Record results from each toss in the appropriate column.	
heads (allele for trait is present)	tails (allele for trait is absent)

Reminder: In autosomal dominant inheritance, if the allele is present, the trait will be present.

Figure 2-4 A coin-toss modeling experiment

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(the second generation)? Use the data from the coin test to support your conclusion. What about the results in the third generation of Pedigree I?

6. Examine Pedigrees I and J again carefully and summarize your observations on your worksheet.

   a. Indicate whether your tests confirm or refute the pattern you hypothesized. Record your response as your "conclusions." *(Hint: Your conclusion could be in the form of a question.)*

   b. If your earlier choice was refuted, can you now propose a new explanation? If so, record it under "Hypothesis 2" on your worksheet. If not, do not worry. Steps 7-9 may help you.

7. Use Questions 7a and 7b to help you find a new explanation.

   a. Examine each instance where the trait is passed to offspring. What do you observe about the source of the inherited trait?

   b. Mendelian genetics assumes that in all cases each parent contributes equally to the genotype of the offspring. Do the data shown in Pedigrees I and J demonstrate this idea?

Modify your conclusions or propose a new hypothesis if your ideas have changed.

As a final attempt to build a new explanation, use Questions 8 and 9 to guide your thinking. When you have recorded your best explanation, continue to the Analysis. (Your explanation may be incomplete. What is important is that you justify your reasoning with evidence.)

8. Could the inheritance of an allele carried on the X or Y chromosome explain the pattern of inheritance in Pedigrees I and J? Explain your response.

9. Consider the four patterns of inheritance in Figure 2-2. What do they assume about the location of genetic material in the cell?

   a. In humans, sperm cells and egg cells transmit genetic information to offspring. How do these cells differ?

   b. In addition to a complete set of chromosomes (46), what does the developing zygote need to grow and develop? *(Hint: What structures are in the cytoplasm?)*

Analysis

1. Read the two articles your teacher distributes. What bearing does the information in the articles have on your explanation of Pedigrees I and J?

2. What lasting scientific knowledge about inheritance did you use in this activity?

3. What new explanations for inheritance did you use in this activity?

4. What methods of science did you use in this activity?

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Activity 3
Clues and Discoveries in Science

How do you know that a new scientific idea is correct? Lots of people have good ideas about how to explain what they observe in living systems, but a good idea alone is not enough. Scientists constantly have to decide whether a new idea is valid, and they do so by using the requirements of science. To meet these criteria, a good idea must be based on logical reasoning, and it must be tested, preferably many times and in many different ways. A scientist draws an idea (hypothesis) from early observations of a problem and then collects evidence to determine whether the idea is scientifically valid. If the hypothesis seems to be valid, the scientist will share it with other scientists. They, in turn, may repeat the tests to see whether the evidence is reproducible, or they may add new lines of evidence from different tests. If enough evidence accumulates, the scientific community accepts the hypothesis as valid and it becomes part of the established body of scientific knowledge. In simple terms, people then refer to the new idea as part of "what they know about genetics."

This approach to building an explanation for a natural process sounds fairly simple, but it can be complicated. For example, how do you tell the difference between discovery of a new process and misinterpretation of data? Such a debate arose in genetics among people who studied two inherited disorders, Huntington disease (HD) and myotonic dystrophy (DM). In this activity, you will step into the shoes of the scientists involved in this debate and use the requirements of science to follow the history of this intriguing investigation. Read the descriptions of HD and DM in Figures 3-1 and 3-2 if you are not familiar with these disorders.

Procedure

Part I: Identifying the Mystery

1. The dialogue below takes you back in history to 1957. Read the dialogue and then answer Questions 1a-1e.

Note that in this dialogue we use the term "chorea"; this name for HD was the common term used in the 1950s.

The year is 1957. This dialogue is part of a discussion that might have taken place between a physician and a geneticist; we will call them Dr. A and Dr. B. As you read their discussion, think about *why* they have different views.

Dr. A: "I've been seeing a patient named Allen who may have Huntington's chorea. If so, I think he is a good example of genetic anticipation."

Dr. B: "You mean that this disease runs in his family, but is showing up at an earlier age in Allen than it did in his parents or grandparents?"

Dr. A: "Exactly. Allen is only 40, and already he has short periods of memory loss and sudden problems with awkward movement of his legs. When I interviewed him, I learned that his mother died when she was 65, but, starting at age 55, people who knew her said she was a bit 'odd' in her thinking. She spent her last five years in a wheelchair, suffering from severe muscle and movement problems. She appeared to have Huntington's chorea."

Dr. B: "But that doesn't prove that genetic anticipation is a real phenomenon. What do you know about Allen's maternal grandparents and great-grandparents?"

Dr. A: "Not much. His mother's mother died when she was very young, during childbirth, so all we know is that she did not show signs of Huntington's chorea up to the age of 24. Allen's grandfather lived to be about 70, but Allen knew nothing about his general health. But you *know* geneticists have reported cases of anticipation for years. What about Dr. Bell's discussion of it in her 1947 publication in *The Treasury of Human Inheritance*? She makes a good argument for genetic anticipation in another genetic disease, myotonic dystrophy."

Dr. B: "You mean her mention that patients in an earlier generation of a known pedigree generally had only mild symptoms, such as cataracts, when they were middle-aged, while — "

Dr. A: "— while their children and grandchildren had muscle wasting and mental illness, more severe in each subsequent generation — an example of genetic anticipation."

Dr. B: "(Laughing) Perhaps. But you haven't mentioned a different publication from that year, the one by that geneticist Penrose. He mentions Bell's work and reports from other geneticists, but he points out that simple Mendelian

Figure 3-1 Huntington Disease (HD): Summary of Symptoms

Huntington disease came to public attention in the 1940s when the well-known folk singer Woody Guthrie began to show symptoms of this fatal genetic disorder. Huntington disease received notoriety again in the 1980s and early 1990s when researchers, including Dr. Nancy Wexler, hunted for and located the mutant gene that causes HD. Dr. Wexler caught the public's interest in part because she had a direct and personal concern with this genetic killer: her mother died of Huntington disease, so Dr. Wexler knew she was at risk.

HD is inherited as an autosomal dominant disorder. It is rare, occurring at a frequency of about 1/20,000 in Western countries and less often in Asia and elsewhere. The onset of symptoms generally occurs in adulthood, but the age varies among individuals and between generations of affected people. The disease involves neurological function, and early symptoms include twitchy muscles, awkwardness of movement, and memory dysfunction. Eventually symptoms become severe, and death results. The gene is located on chromosome 4.

Figure 3-2 Myotonic Dystrophy (DM): Summary of Symptoms

Myotonic dystrophy is a fairly rare inherited human disorder that occurs in 1/8000 Caucasians and even less frequently in other groups. DM shows a large degree of variability in the type and severity of symptoms. The age of onset may vary from one family member to another of those affected. In its mildest forms, DM leaves the individual asymptomatic until late in adulthood. Then it may show up only as cataracts on the eyes, which affect vision. Because cataracts are not uncommon in elderly people, many individuals with extremely mild DM symptoms may not realize they have inherited this disorder. (Conversely, just because a relative of yours has had cataracts, do not assume that DM occurs in your family.)

More serious symptoms include muscle abnormalities such as a breakdown of muscle tissue and the inability to relax a muscle after it has been contracted. Other symptoms involve damage to the heart or the sexual organs (gonads). Some individuals who have inherited DM show mental retardation as children. A less severe form results in unusual drowsiness and inattentiveness in adults.

Myotonic dystrophy is inherited as an autosomal dominant disorder. The gene is located on chromosome 19.

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inheritance of a dominant characteristic won't result in the increasing problems of the disease in children and grandchildren of someone who has the disease gene."

Dr. A: "Then how do you explain the observed anticipation?"

Dr. B: "I don't, at least, not yet. It may be an error in observation. Besides, I would need more data."

References:
J. Bell (1947), Dystrophia myotonica and allied disease, in *The Treasury of Human Inheritance IV. Nervous diseases and muscular dystrophies*, vol 5, p. 343; and L.S. Penrose (1947), The problem of anticipation in pedigrees of dystrophia myotonica, *Annals of Eugenics* 14:125-132.

Think about the dialogue as you respond to these questions.

a. What is genetic anticipation?

b. Why does Dr. B. want more data?

c. Dr. B. refers to "an error in observation." How might such an error arise? What could be done about it?

d. What have you learned about dominant inheritance? Why is genetic anticipation *not* explained by this genetic concept?

e. What else could be done to solve this mystery?

Part II: Gathering Clues to the Mystery

The year is 1977. You have collected interview data from many of the members of Allen's family. Use what you know from the dialogue and from this new case-history information to answer the Challenge Questions in Figure 3-3.

2. Each team has different clues obtained from case histories. You only have a few minutes to consider your team's clues before you pool your information with that from other teams.

3. Follow your teacher's instructions about how to report your preliminary findings.

Figure 3-3 Challenge Questions

Scientists had to think about genetic anticipation in several steps. They needed to break the problem into addressable questions.

- What evidence do you have to support or refute the existence of genetic anticipation?
- Do you have evidence that supports a possible explanation for the genetic mechanism that causes anticipation? If yes, explain.

4. What does this evidence tell you about the Challenge Questions in Figure 3-3 (if anything)?

Now the year is 1997. Molecular biologists have devised a test to identify the mutant gene for HD and to determine some of its special properties. In addition, many of the family members have had the test; in some cases blood samples stored from older, deceased members were tested. Your teacher will supply you with an article that describes the new molecular test for HD and the results of this test when performed on the members of Allen's family.

5. Read the article and record the information from the HD molecular clues on your HD pedigree. Report this information to the class when your teacher instructs you to do so.

6. Why does each person tested have *two* repeat numbers?

7. Using this new evidence, once again address the Challenge Questions in Figure 3-3.

8. One of the strengths of a good scientific explanation is that it is supported by multiple lines of evidence. Use a set of clues for a different family to look for additional evidence that supports your answers to the preceding questions.

Part IV: Discovering the History of Genetic Anticipation

The sequence of discovery demonstrated by the clues you used reflects the history of discovery about

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genetic anticipation. Use the brief scenes (vignettes) that your teacher will give you to build a more complete picture of the history of discovery about HD and genetic anticipation. As you read, try to determine at what point in the sequence the opening dialogue between the fictitious Drs. A. and B. might have taken place. What additional vignettes might follow these in the future?

9. Read the vignettes and discuss with your teammates what they tell you about the history of our understanding of HD.

10. As a team, draw up a brief outline of the history of discovery about HD.

11. Individually, write a new vignette that represents what you predict may be the next level of discovery about HD.

12. After you complete the vignette, explain the aspects of science on which you based your predictions.

Analysis

1. What is the relationship between the number of trinucleotide repeats in the mutant HD or DM gene and the resulting phenotype?

2. How does what you know about genetic anticipation contrast with the traditional, Mendelian view of autosomal dominant inheritance?

3. How have you used the methods of science in this activity?

4. Write a vignette (brief scene or part of a story) about the future health of Peter, Cathy, and Sean. Use your case-history data and the article you read to support your description.

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Activity 4 Should Teenagers Be Tested for the Mutant HD Gene?

How should you go about making good choices about important issues in life? Should you base your decisions on a whim, a coin toss, or a call to a psychic hot line? Or should you rely on well-informed, well-reasoned analysis? Scientific reasoning is a disciplined way to understand events in the natural world. Similarly, a discussion of ethical issues brings reason and discipline to decisions that involve preferences based on values. We draw our values from many sources, including history, law, religion, and family. Part of the task of ethics is to identify these values clearly and to show why others should regard them as important. A discussion of ethical issues may apply to what we do as individuals or to how public policy is made. In this activity, you will use the principles of sound decision-making and ethics to decide whether a policy that excludes teenagers from genetic testing is a good public policy.

Procedure

Part I: Identifying the Issue

1. People often express their opinions or concerns through a letter to the editor of a newspaper. Read the letter shown in Figure 4-1.
2. Assume that a change in policy would give *parents* the right to request an HD test for a person who is under 18 years of age. Decide whether you think the policy of not testing minors should stand or be changed. Register your vote when your teacher polls the class.

Part II: Using Ethical Decision-making

3. Form teams as directed by your teacher to conduct a discussion of the ethical issues in the letter. *Regardless of your personal opinion* on this issue, work with your team to draw up two lists of opposing ideas about this policy, using the worksheet provided by your teacher. In the left column, list reasons the current policy is good. In the right column, list reasons the policy should change or why the new policy is better. Record all of your team's ideas.
4. Present your team's ideas to the class. Add notes to your own worksheet of new ideas that arise during the discussion with other teams.
5. Consider the discussion of ethical issues performed by the class and vote again. Is the current policy good and worth maintaining, or should it be changed so that parents of minors at risk for HD can have their children tested?

Figure 4-1 Letter to the editor of a city newspaper

Ms. Candice Girard, Editor
The News and Times

Dear Ms. Girard:

My family faces a very difficult health problem. My husband is only 35 years old and has been diagnosed with a rare, inherited genetic disorder known as Huntington disease. He already shows some of the symptoms and, unless gene therapy or some other medical treatment is developed in the next 10 years or so, he will slowly get worse and finally die from this condition.

As if this situation weren't bad enough, we also have to worry whether our young son, who is a minor, has inherited this mutation. He has a 50:50 chance of having gotten the mutant gene from his father. As of now, our son is healthy, but if he has this mutation the disorder will appear after he is an adult. A genetic test would tell us the answer; either it would relieve us of the burden of worry or tell us that our son, too, will face the same ordeal as his father. Either way, we would be rid of this awful uncertainty. The test could help predict roughly how soon symptoms are likely to show up.

We want to have this test done, but the geneticist will not order it. He says that most testing centers have a policy of not testing people under the age of 18 as long as they show no symptoms. The main reason for this policy is to protect young people. There's no medical advantage to testing—no treatment or preventive measure. Knowing could be emotionally harmful. People may become depressed or worry about getting insurance. The geneticist says the current policy protects the youth's right to decide *after* becoming an adult, rather than having a parent decide now.

I'm not sure I can bear not knowing. Think what a relief it would be if we found out that our son has not inherited the mutation. As he sees his father grow more ill, we could reassure our son that the same thing *won't* happen to him. It's just as likely that the test will be negative as positive.

Do your readers think the policy should change to allow parents to make this request for their children?

Sincerely,

Jean W.

Analysis

1. Given that there is no treatment at present for HD, how does acquiring scientific evidence about the presence or absence of the HD mutation (from a genetic test) change the discussion of the issue?

2. What additional social and ethical issues might new knowledge in genetics raise?

3. As a homework assignment, write a response to Jean W.'s letter. You might let her know whether *you* would choose to be tested, and why. In your letter, describe what scientific evidence from a genetic test will tell you and how that information affects your choice. In addition, show how the discussion of ethical issues that your class conducted has influenced your ideas.

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Activity 5
What Do We Know? How Do We Know It?

"They say getting too much sun can give you cancer."

Who are "they"? Should you believe what "they" say, and, if so, should you change your behavior in any way?

All of us must assume responsibility for making decisions that affect us and others, but this responsibility does not guarantee that we will make good decisions. That skill requires lots of practice and careful reasoning, and it requires intelligent analysis of information. For health-related comments, such as the preceding quote, you should consider the scientific validity of the statement to determine whether you think the statement is reliable. Even if you decide that it is reliable, the choice of what to do about it still remains yours. (Is having a tan or relaxing in the sunlight worth the risk of getting skin cancer? How can you reduce the risk?) Whatever you decide, the ability to determine the scientific validity of a popular claim is a valuable skill for any person.

As you work through this last activity, you will evaluate what you have learned in the previous activities.

PROCEDURE

Part I: Critique of Popular Media Topics

You are going to critique claims from the popular press for their scientific validity.

1. Recall from the previous activities the requirements of a good scientific explanation and list them.

2. Join your team and look at the articles the team members have collected. Choose one to present to the class. Discuss the reasons the article gives (if any) to support the claim being reported. (Be prepared to list the idea from the article and to give supporting evidence, if any, on a chart in the classroom. You have 5-10 minutes to prepare.)

3. When your teacher gives the signal, move with your team to one chart and quickly list the claim

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from your team's article and indicate the source. Next show *why* this claim is supposed to be correct, according to the article. Spend only 2 minutes at this task.

4. Move with your team to the next chart. Read the ideas listed by the previous team and critique this claim for its scientific validity. You have 3 minutes.

Part II: Analysis

Respond to the following questions as the class discusses the charts.

1. What is the difference between a belief and an explanation that meets the requirements of science?
2. Based on the information presented on the charts, are any of the claims scientifically valid?
3. How could your actions be influenced by knowing whether a claim is scientifically valid?
4. Many health or science claims have significance in society because they are popular; that is, they have emotional appeal for many people. How would the work of scientists be different if scientific explanations were *voted upon for popularity* rather than held up to the scientific standards discussed in this module?

Part III: Assessment

Respond to the following questions or assignments according to your teacher's instructions.

1. Recall your experiences from the module as you answer the following questions:
   a. What does science try to do?
   b. How do we know that our scientific explanations are on the right track?
   c. What counts as evidence in science?
   d. What makes science objective?
   e. How and why does scientific knowledge change?
   f. What is the difference between pseudoscience and science?
2. The previous activities used genetics examples to show how science works.
   a. What genetics concepts did you discuss in this module?
   b. Were any of the genetics concepts you listed new to you? Identify them and indicate their relationship to earlier knowledge.
3. How are science and society related? Give at least two examples.
4. Your job is to critique two claims that you see reported in popular media. One should be a science or health report that you consider to be scientifically reliable, and the other should be a claim that you think is not scientifically substantiated. (Remember, a claim could be based on a correct idea but reported poorly, making the *report* scientifically unsound.)

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